Kronos LV-T

Cardiac Resynchronization Therapy - Defibrillator

Technical Manual

BIOTRONIK

X-ray Identification

Kronos LV-T
Cardiac Resynchronization Therapy - Defibrillator

Inside the housing, top left-hand side:

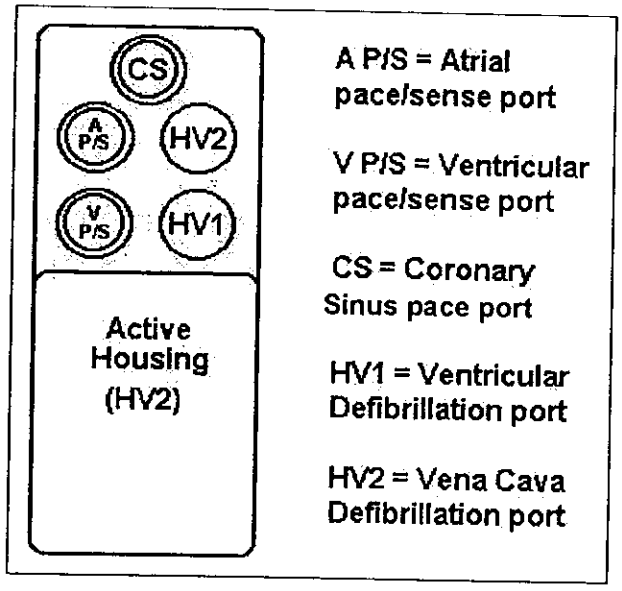
Year of manufacture

X-Ray identification

CAUTION

Federal (U.S.A.) law restricts this device to sale by, or on the order of, a physician.

Contents



Kronos LV-T Specifications and Description

Battery Voltage:	6.3 Volts
Maximum Shock Energy:	30 joules
Defibrillation Lead Ports	Two DF-1 (3.2 mm)
Pacing Lead Ports	Three IS-1 (3.2 mm)
Dimension:	55 x 70 x 13 mm
Volume:	41 cc
Mass:	75 g
Housing Material:	Titanium
Header Material:	Epoxy Resin
Sealing Plug Material:	Silicone
Battery Composition	Li / MnO_2

1. General

1.1 System Description

The Kronos LV-T Cardiac Resynchronization Therapy-Defibrillator (CRT-D) provides Cardiac Resynchronization Therapy (CRT) through biventricular pacing, detects and treats ventricular tachyarrhythmias and provides rate adaptive bradycardia pacing support. The CRT-D is designed to collect diagnostic data to aid the physician's assessment of a patient's condition and the performance of the implanted device.

The Kronos LV-T CRT-D provides biventricular pacing through a fifth header port (CS port in previous figure) utilizing an IS-1 unipolar connector for the left ventricular (LV) channel. The Kronos LV-T provides CRT in a "shared-ring" configuration with both the RV and LV outputs tied together and are only programmable to a single value for both outputs. Internal circuitry delivers ventricular pacing pulses simultaneously to the right / left ventricular lead tips (cathode) with the ring of the right ventricular lead as the other electrode (anode). Ventricular sensing uses only the right ventricular lead tip and ring to avoid sensing of ventricular activity twice (double counting) during a single cardiac cycle in patients with a wide QRS complex. This is particularly important to avoid inappropriate delivery of ventricular therapy.

The Kronos LV-T CRT-D can provide triggered biventricular pacing. The "triggering function" is designed to ensure biventricular pacing therapy is delivered during rapidly conducted atrial arrhythmias, such as atrial fibrillation. This function triggers pacing delivery (Vp) in the ventricles after intrinsic sensing in the right ventricle. The trigger function is only available in the biventricular pacing configuration, e.g., a forced ventricular pace (Vp) after previous sensing (right ventricular sense event).

The Kronos LV-T provides therapy for ventricular tachyarrhythmias with a sophisticated range of programmable antitachycardia pacing (ATP), and/or defibrillation therapy. The shock polarity and energy may be programmed to tailor the therapy to appropriately treat each patient's tachyarrhythmias. The CRT-D provides biphasic shocks with programmable energies from 1 to 30 joules.

- The Kronos LV-T provides dual chamber rate adaptive bradycardia pacing support. The CRT-D uses atrial and ventricular sensing/pacing leads to provide enhanced atrial and ventricular tachyarrhythmia discrimination through BIOTRONIK's SMART Detection™ algorithm.
- The Kronos LV-T also includes the functionality of BIOTRONIK's Home Monitoring system. Home Monitoring enables automatic exchange of information about a patient's cardiac status from the implant to the physician remotely.

The Kronos LV-T has two DF-1 defibrillation/ cardioversion and three IS-1 pacing/sensing header ports. IS-1 refers to the international standard whereby leads and generators from different manufacturers are assured a basic fit [Reference ISO 5841-3:1992]. DF-1 refers to the international standard for defibrillation lead connectors [Reference ISO 11318:1993].

External devices that interact with and test the implantable devices are also part of the CRT-D System. These external devices include the ICS 3000 Implant Control System, TMS 1000^{PLUS} Tachyarrhythmia Monitoring System and the EPR 1000^{PLUS} Programming and Monitoring System. These programmers are used to interrogate and program the CRT-D.

1.2 Indications and Usage

The Kronos LV-T CRT-D is indicated for use in patients with all of the following conditions:

- Indicated for ICD therapy
- Receiving optimized and stable Congestive Heart Failure (CHF) drug therapy
- Symptomatic CHF (NYHA Class III/IV and LVEF ≤ 35%); and
- Intraventricular conduction delay (QRS duration ≥130 ms)

1.3 Contraindications

The Kronos LV-T CRT-D is contraindicated for use in patients with the following conditions:

- Patients whose ventricular tachyarrhythmias may have transient or reversible causes such as:
  - Acute myocardial infarction
  - Digitalis intoxication
  - Drowning
  - Electrocution
  - Electrolyte imbalance
  - Hypoxia
  - Sepsis
- Patients with incessant ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Patients whose only disorder is bradyarrhythmias or atrial arrhythmias

1.4 Warnings and Precautions

MRI (Magnetic Resonance Imaging) - Do not expose a patient to MRI device scanning. Strong magnetic fields may damage the device and cause injury to the patient.

Electrical Isolation - To prevent inadvertent arrhythmia induction, electrically isolate the patient during the implant procedure from potentially hazardous leakage currents.

Lead Systems – BIOTRONIK CRT-Ds maybe implanted with any legally marketed, compatible ICD lead. Compatibility is defined as:

- IS-1 pacing and sensing connector(s)
- DF-1 shock coil connector(s)
- Integrated or dedicated bipolar pacing and sensing configuration
- Active or passive fixation technology
- Single or dual defibrillation shock coil (s)
- High energy shock accommodation of at least 30 joules
- Insertion and withdrawal forces as specified by ISO 5841-3 (IS-1) and ISO 11318:1993 (E) DF-1

The following leads were evaluated in a retrospective study with BIOTRONIK's ICDs:

- Medtronic Sprint 6932
- Medtronic Sprint 6943
- Medtronic Sprint Quattro 6944
- Medtronic Transvene RV 6936
- St. Jude (Ventritex) TVL- ADX 1559
- St. Jude SPL SP02
- Guidant Endotak DSP
- Guidant Endotak Endurance EZ, Endotak Reliance
- Guidant (Intermedics) 497-24.

The following leads were bench tested for compatibility with BIOTRONIK's ICDs:

- Guidant Endotak Endurance "CPI 0125"
- Guidant Endotak Reliance 0148
- Medtronic Sprint 6932
- Medtronic Sprint 6942
- Medtronic Sprint 6943
- Medtronic Sprint 6945
- Medtronic Sprint Quattro 6944
- St. Jude Riata 1571/65
- St. Jude SPL SPO1

Resuscitation Availability - Do not perform induction testing unless an alternate source of patient defibrillation such as an external defibrillator is readily available. In order to implant the CRT-D system, it is necessary to induce and convert the patient's ventricular tachyarrhythmias.

Unwanted Shocks – Always program Therapy status to OFF prior to handling the device to prevent the delivery of serious shocks to the patient or the person handling the device during the implant procedure.

Rate-Adaptive Pacing – Use rate-adaptive pacing with care in patients unable to tolerate increased pacing rates.

High Output Settings – High ventricular or biventricular pacing voltage settings may reduce the life expectancy of the pulse generator to less than 1 year. Programming of pulse amplitudes, higher than 4.8V, in combination with long pulse widths and/or high pacing rates may lead to early activation of replacement indicators.

Triggered Pacing – It is possible that activation of the Bi-V/T triggered pacing mode could lead to a VT/VF arrhythmia in the case that a left ventricular ectopic beat with abnormally prolonged conduction times is sensed by the right ventricle. This situation could lead to a pacing pulse being delivered in the vulnerable period of ventricular repolarization. To minimize this rare pro-arrhythmic risk, measure the conduction time of left ventricular paced beats to the right ventricular sense marker using the IEGM features. If an excessive conduction delay (>150 ms) is present, the Bi-V/T triggered pacing mode should not be activated.

1.4.1 Sterilization, Storage, and Handling

Device Packaging - Do not use the device if the device's packaging is wet, punctured, opened or damaged because the integrity of the sterile packaging may be compromised. Return the device to BIOTRONIK.

Re-sterilization - Do not re-sterilize and re-implant explanted devices.

Storage (temperature) - Store the device between 5° to 55°C (41° - 131° F) because temperatures outside this range could damage the device.

Storage (magnets) - To avoid damage to the device, store the device in a clean area, away from magnets, kits containing magnets, and sources of electromagnetic interference (EMI).

Temperature Stabilization - Allow the device to reach room temperature before programming or implanting the device because temperature extremes may affect initial device function.

Use Before Date - Do not implant the device after the USE BEFORE DATE because the device may have reduced longevity.

1.4.2 Device Implantation and Programming

Blind Plug - A blind plug must be inserted and firmly connected into any unused header port to prevent chronic fluid influx and possible shunting of high energy therapy.

Capacitor Reformation - Infrequent charging of the high voltage capacitors may extend the charge times of the CRT-D. The capacitors are reformed automatically at least every 85 days and may be reformed manually. For further information, please refer to Section 2.9.4, Capacitor Reforming.

Connector Compatibility - CRT-D and lead system compatibility should be confirmed prior to the implant procedure. Consult your BIOTRONIK representative regarding lead/pulse generator compatibility prior to the implantation of a CRT-D system. For further information, please refer to Appendix A.

ERI (Elective Replacement Indicator) - Upon reaching ERI, the battery has sufficient energy remaining to continue monitoring for at least three months and to deliver a minimum of six 30 joule shocks. After this period, all tachyarrhythmia detection and therapy is disabled. Bradycardia functions are still active at programmed values until the battery voltage drops below 3.0 volts.

Magnets - Positioning of a magnet or the programming wand over the CRT-D will suspend tachycardia detection and treatment. The minimum magnet strength required to suspend tachycardia treatment is 1.8 mT. When the magnet strength decreases to less than 1 mT, the reed contact is reopened.

Programmed Parameters – Program the device parameters to appropriate values based on the patient's specific arrhythmias and condition.

Programmers - Use only BIOTRONIK programmers to communicate with the device (ICS 3000, TMS 1000^{PLUS}, or EPR 1000^{PLUS}).

Sealing System - Failure to properly insert the torque wrench into the perforation at an angle perpendicular to the connector receptacle may result in damage to the sealing system and its self-sealing properties.

Programming Wand Separation Distance – The wand must not be placed closer than 2 cm to the device (implanted or out of the box). Programming wand distance closer than 2 cm may damage the device.

Defibrillation Threshold - Be aware that the changes in the patient's condition, drug regimen, and other factors may change the defibrillation threshold (DFT) which may result in non-conversion of the arrhythmia post-operatively. Successful conversion of ventricular fibrillation or ventricular tachycardia during arrhythmia conversion testing is no assurance that conversion will occur post-operatively.

Manual Shocks – User-commanded shocks may be withheld if the CRT-D is already busy processing a manual command or the Battery Status is low.

Charge Time - When preparing a high energy shock the charge circuit stops charging the capacitors after 16 seconds, and delivers the stored energy as shock therapy. After the device reaches ERI the stored energy may be less than 30 joules per shock.

Shock Impedance - If the shock impedance is less than twenty-five ohms, reposition the lead system to allow a greater distance between the electrodes. Never implant the device with a lead system that has measured shock impedance as less than twenty-five ohms. Damage to the device may result.

1.4.3 Lead Evaluation and Connection

Capping Leads - If a lead is abandoned rather than removed, it must be capped to ensure that it is not a pathway for currents to or from the heart.

Gripping Leads - Do not grip the lead with surgical instruments or use excessive force or surgical instruments to insert a stylet into a lead.

Kinking Leads - Do not kink leads. This may cause additional stress on the leads that can result in damage to the lead.

Liquid Immersion - Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Short Circuit - Ensure that none of the lead electrodes are in contact (a short circuit) during delivery of shock therapy as this may cause current to bypass the heart or cause damage to the CRT-D system.

Far-field sensing of signals from the atrium in the ventricular channel or ventricular signals in the atrial channel should be avoided by appropriate lead placement, programming of pacing/sensing parameters, and maximum sensitivity settings. If it is necessary to modify the Far Field Blanking parameter, the parameter should be lengthened only long enough to eliminate far-field sensing as evidenced on the IEGMs. Extending the parameter unnecessarily may cause under sensing of actual atrial or ventricular events.

Suturing Leads - Do not suture directly over the lead body as this may cause structural damage. Use the appropriate suture sleeve to immobilize the lead and protect it against damage from ligatures.

Tricuspid Valve Bioprosthesis - Use ventricular transvenous leads with caution in patients with a tricuspid valvular bioprosthesis.

Setscrew Adjustment – Back-off the setscrew(s) prior to insertion of lead connector(s) as failure to do so may result in damage to the lead(s), and/or difficulty connecting lead(s).

Cross Threading Setscrew(s) – To prevent cross threading the setscrew(s), do not back the setscrew(s) completely out of the threaded hole. Leave the torque wrench in the slot of the setscrew(s) while the lead is inserted.

Tightening Setscrew(s) – Do not overtighten the setscrew(s). Use only the BIOTRONIK supplied torque wrench.

Sealing System – Be sure to properly insert the torque wrench into the perforation at an angle perpendicular to the connector receptacle. Failure to do so may result in damage to the plug and its self-sealing properties.

1.4.4 Follow-up Testing

Defibrillation Threshold - Be aware that changes in the patient's condition, drug regimen, and other factors may change the defibrillation threshold (DFT), which may result in non-conversion of the arrhythmia post-operatively. Successful conversion of ventricular fibrillation or ventricular tachycardia during arrhythmia conversion testing is no assurance that conversion will occur post-operatively.

Resuscitation Availability - Ensure that an external defibrillator and medical personnel skilled in cardiopulmonary resuscitation (CPR) are present during post-implant device testing should the patient require external rescue.

Safe Program – Within the EP Test screen, pressing the "Safe Program" key on the programmer head does not immediately send the safe program to the CRT-D. Pressing the "Safe Program" key activates the emergency function screen, but an additional screen touch is required to send the safe program to the CRT-D.

1.4.5 Pulse Generator Explant and Disposal

Device Incineration – Never incinerate the CRT-D due to the potential for explosion. The CRT-D must be explanted prior to cremation.

Explanted Devices – Return all explanted devices to BIOTRONIK.

Unwanted Shocks – Always program Therapy status to OFF prior to handling the device to prevent the delivery of serious shocks to the patient or the person handling the device during the implant procedure.

1.4.6 Hospital and Medical Hazards

Electromagnetic interference (EMI) signals present in hospital and medical environments may affect the function of any CRT-D, ICD or pacemaker. The CRT-D is designed to selectively filter out EMI noise. However, due to the variety of EMI signals, absolute protection from EMI is not possible with this or any other CRT-D or ICD.

The CRT-D system should have detection and therapy disabled prior to performing any of the following medical procedures. In addition, the CRT-D should be checked after the procedures to assure proper programming:

Diathermy - Diathermy therapy is not recommended for CRT-D patients due to possible heating effects of the pulse generator and at the implant site. If diathermy therapy must be used, it should not be applied in the immediate vicinity of the pulse generator or lead system.

Electrocautery - Electrosurgical cautery could induce ventricular arrhythmias and/or fibrillation, or may cause device malfunction or damage. If use of electrocautery is necessary, the current path and ground plate should be kept as far away from the pulse generator and leads as possible (at least 6 inches (15 cm)).

External Defibrillation - The device is protected against energy normally encountered from external defibrillation. However, any implanted device may be damaged by external defibrillation procedures. In addition, external defibrillation may also result in permanent myocardial damage at the electrode-tissue interface as well as temporary or permanent elevated pacing thresholds. When possible, observe the following precautions:

- Position the adhesive electrodes or defibrillation paddles of the external defibrillator anterior-posterior or along a line perpendicular to the axis formed by the implanted device and the heart.
- Set the energy to a level not higher than is required to achieve defibrillation.
- Place the paddles as far as possible away from the implanted device and lead system.
- After delivery of an external defibrillation shock, interrogate the CRT-D to confirm device status and proper function.

Lithotripsy - Lithotripsy may damage the CRT-D. If lithotripsy must be used, avoid focusing near the CRT-D implant site.

MRI (Magnetic Resonance Imaging) - Do not expose a patient to MRI device scanning. Strong magnetic fields may damage the device and cause injury to the patient.

Radiation - High radiation sources such as cobalt 60 or gamma radiation should not be directed at the pulse generator. If a patient requires radiation therapy in the vicinity of the pulse generator, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.

Radio Frequency Ablation - Prior to performing an ablation procedure, deactivate the CRT-D during the procedure. Avoid applying ablation energy near the implanted lead system whenever possible.

1.4.7 Home and Occupational Hazards

Patients should be directed to avoid devices that generate strong electromagnetic interference (EMI) or magnetic fields. EMI could cause device malfunction or damage resulting in non-detection or delivery of unneeded therapy. Moving away from the source or turning it off will usually allow the CRT-D to return to its normal mode of operation.

The following equipment (and similar devices) may affect normal CRT-D operation: electric arc or resistance welders, electric melting furnaces, radio/television and radar transmitters, power-generating facilities, high-voltage transmission lines, and electrical ignition systems (of gasoline-powered devices) if protective hoods, shrouds, etc., are removed.

1.4.8 Cellular Phones

Testing has indicated there may be a potential interaction between cellular phones and BIOTRONIK CRT-D systems. Potential effects may be due to either the cellular phone signal or the magnet within the telephone and may include inhibition of therapy when the telephone is within 6 inches (15 centimeters) of the CRT-D, when the CRT-D is programmed to standard sensitivity.

Patients having an implanted BIOTRONIK CRT-D who operate a cellular telephone should:

- Maintain a minimum separation of 6 inches (15 centimeters) between a hand-held personal cellular telephone and the implanted device.
- Set the telephone to the lowest available power setting, if possible.
- Patients should hold the phone to the ear opposite the side of the implanted device. Patients should not carry the telephone in a breast pocket or on a belt over or within 6 inches (15 centimeters) of the implanted device as some telephones emit signals when they are turned ON, but not in use (i.e., in the listen or stand-by mode). Store the telephone in a location opposite the side of implant.

Based on results to date, adverse effects resulting from interactions between cellular telephones and implanted CRT-Ds have been transitory. The potential adverse effects could include inhibition or delivery of additional therapies. If electromagnetic interference (EMI) emitting from a telephone does adversely affect an implanted CRT-D, moving the telephone away from the immediate vicinity of the CRT-D should restore normal operation. A recommendation to address every specific interaction of EMI with implanted CRT-D is not possible due to the disparate nature of EMI.

1.4.9 Electronic Article Surveillance (EAS)

Equipment such as retail theft prevention systems may interact with pulse generators. Patients should be advised to walk directly through and not to remain near an EAS system longer than necessary.

1.4.10 Home Appliances

Home appliances normally do not affect CRT-D operation if the appliances are in proper working condition and correctly grounded and shielded. There have been reports of the interaction of electric tools or other external devices (e.g. electric drills, older models of microwave ovens, electric razors, etc.) with CRT-Ds when they are placed in close proximity to the device.

1.4.11 Home Monitoring

Patient's Ability - Use of the Home Monitoring system requires the patient and/or caregiver to follow the system instructions and cooperate fully when transmitting data.

If the patient cannot understand or follow the instructions because of physical or mental challenges, another adult who can follow the instructions will be necessary for proper transmission.

Use in Cellular Phone Restricted Areas - The mobile patient device (transmitter/receiver) should not be utilized in areas where cellular phones are restricted or prohibited (i.e., commercial aircraft).

Event-Triggered Report – A timely receipt of the event report cannot be guaranteed. The receipt is also dependent on whether the patient was physically situated in the required coverage range of the patient device at the time the event information was sent.

Not for Diagnosis - The data transmitted by Home Monitoring are not suitable for diagnosis, because not all information available in the implant is being transmitted.

Follow-Ups - The use of Home Monitoring does not replace regular follow-up examinations. Therefore, when using Home Monitoring, the time period between follow-up visits may not be extended.

1.5 Potential and Observed Effects of the Device on Health

1.5.1 Potential Adverse Events

The following are possible adverse events that may occur relative to the implant procedure and chronic implant of the CRT-D:

- Air embolism
- Allergic reactions to contrast media
- Arrhythmias
- Bleeding
- Body rejection phenomena
- Cardiac tamponade
- Chronic nerve damage
- Damage to heart valves
- Device migration
- Elevated pacing thresholds
- Extrusion
- Fluid accumulation
- Hematoma
- Infection
- Keloid formation
- Lead dislodgment
- Lead fracture/ insulation damage
- Lead-related thrombosis
- Local tissue reaction / fibrotic tissue formation
- Muscle or nerve stimulation
- Myocardial damage
- Myopotential sensing
- Pacemaker mediated tachycardia
- Pneumothorax
- Pocket erosion
- Thromboembolism
- Undersensing of intrinsic signals
- Venous occlusion
- Venous or cardiac perforation

In addition, patients implanted with the CRT-D system may have the following risks. These are the same risks relate with implantation of any CRT-D system:

- Acceleration of arrhythmias (speeding up heart rhythm caused by the CRT-D)
- Dependency
- Depression
- Fear of premature battery depletion (fear that battery will stop working before predicted time)
- Fear of shocking while awake
- Fear that shocking ability may be lost
- Anxiety about the CRT-D resulting from frequent shocks
- Imagined shock (phantom shock)
- Inappropriate detection of ventricular arrhythmias
- Inappropriate shocks
- Potential death due to inability to defibrillate or pace
- Shunting current or insulating myocardium during defibrillation with external or internal paddles

There may be other risks associated with this device that are currently unforeseeable.

1.5.2 Observed Adverse Events

Reported Adverse Events are classified as either observations or complications. Complications are defined as clinical events that require additional invasive intervention to resolve. Observations are defined as clinical events that do not require additional invasive intervention to resolve.

1.5.2.1 Kronos LV-T Study

The HOME-CARE Observational study, conducted outside the US on the Kronos LV-T cardiac resynchronization defibrillator (CRT-D) in patients with congestive heart failure (CHF) involved 45 devices implanted with a cumulative implant duration of 202 months (mean implant duration of 4.5 months).

Of the 31 adverse events reported, there have been 26 observations in 23 patients and 5 complications in 3 patients with a cumulative implant duration of 202 months (16.8 patient-years). 6.7% of the enrolled patients have experienced a complication with two patients experiencing 2 separate complications. The rate of complications per patient-year was 0.30. 51% of the enrolled study patients had a reported observation with 3 patients having more than 1 observation. The rate of observations per patient-year is 1.54. Complications and observations for the patient group are summarized in Table 1 and Table 2, respectively.

Table 1: Summary of Complications – Kronos LV-T

Category	Number of Patients	% of Patients	Number	Per patient-year
Left Ventricular Lead Related				
Dislodgement	1	2.2%	1	0.06
No Capture	1	2.2%	1	0.06
Total	**2**	**4.4%**	**2**	**0.12**
ICD Lead Related				
Dislodgement	1	2.2%	1	0.06
Elevated Pacing Threshold	1	2.2%	1	0.06
Total	**2**	**4.4%**	**2**	**0.12**
Unrelated to CRT-D or Leads				
Hemathorax	1	2.2%	1	0.06
Total	**1**	**2.2%**	**1**	**0.06**
Overall Complication Totals	**3**	**6.7%**	**5**	**0.30**

Number of Patients = 45, Number of Patient-Years = 16.8

Table 2: Summary of Observations – Kronos LV-T

Category	Number of Patients	%of Patients	Number	per patient-year
Unsuccessful LV lead implant	8	17.8%	8	0.48
Elevated LV pacing threshold	5	11.1%	5	0.30
Phrenic nerve stimulation	3	6.7%	3	0.18
Elevated DFT measurement	2	4.4%	2	0.12
T-wave oversensing	2	4.4%	2	0.12
Worsening CHF	2	4.4%	2	0.12
Elevated RV pacing threshold	1	2.2%	1	0.06
Hepatitis	1	2.2%	1	0.06
Arrhythmias	1	2.2%	1	0.06
Cardiac Decompensation	1	2.2%	1	0.06
All Observations	**23**	**51.1%**	**26**	**1.54**

Number of Patients = 45, Number of Patient-Years = 16

Two patient deaths were reported during the HOME-CARE Observational Study. One death resulted from worsening heart failure and the second death resulted from cardiogenic shock due to ischemic cardiomyopathy. None of the deaths were related to the implanted CRT-D system. There were no device explants during the HOME-CARE Observational Study.

1.5.2.2 Tupos LV/ATx Study

NOTE:

The clinical study information included in this section and in Section 1.6.2 was performed with the Tupos LV/ATx CRT-D, which is an earlier version of the Kronos LV-T CRT-D. The clinical study data presented here is applicable because the Kronos LV-T is a downsized version of the Tupos LV/ATx. The Kronos LV-T CRT-D is slightly different as compared to the Tupos LV/ATx in the following areas:

- Reduced size from 48 cc to 41 cc
- Addition of Home Monitoring functionality
- Addition of triggered pacing for biventricular pacing modes

The OPTION CRT/ATx study was a prospective, randomized, multi-center study to demonstrate the safety and effectiveness of the investigational Tupos LV/ATx Cardiac Resynchronization Therapy Defibrillator (CRT-D) in patients with congestive heart failure (CHF) and atrial tachyarrhythmias. All patients enrolled into the clinical study were randomly assigned to either the study group or the control group at a 2 to 1 ratio. Patients in the study group were implanted with the Tupos LV/ATx. Patients in the control group were implanted with a legally marketed ICD that provides CRT.

Of the 278 adverse events reported in the Tupos LV/ATx study group, there have been 210 observations in 104 patients and 68 complications in 50 patients with a cumulative implant duration of 1240.4 months (101.9 patient-years). 37.6% of the enrolled study patients have experienced a complication. The rate of complications per patient-year is 0.67. 78.2% of the enrolled study patients have a reported observation. The rate of observations per patient-year is 2.06.

Complications and observations for the Tupos LV/ATx study group are summarized in Table 3 and Table 4. The total number of patients may not equal the sum of the number of patients listed in each category, as an individual patient may have experienced more than one complication or observation.

Table 3: Summary of Complications – Tupos LV/ATx				
Category	**Number of Patients**	**% of Patients**	**Number of Complications**	**Complications per patient-year**
Procedure Related				
Hematoma	4	3.01%	4	0.04
Pneumothorax	2	1.50%	2	0.02
Total	**6**	**4.51%**	**6**	**0.06**
Atrial Lead Related				
Dislodgement	3	2.26%	3	0.03
Total	**3**	**2.26%**	**3**	**0.03**
ICD Lead Related				
High threshold/ No capture	2	1.50%	2	0.02
Diaphragmatic/ Intercostal stimulation (RV)	1	0.75%	1	0.01
Total	**3**	**2.26%**	**3**	**0.03**
LV Lead Related				
High threshold/ Intermittent biventricular capture/ No capture	11	8.27%	12	0.12
Unable to implant lead via coronary sinus	11	8.27%	11	0.11
Dislodgement	4	3.01%	4	0.04
Diaphragmatic/ Intercostal stimulation	1	0.75%	2	0.02
Total	**27**	**20.30%**	**29**	**0.28**

Table 3: Summary of Complications – Tupos LV/ATx				
Category	**Number of Patients**	**% of Patients**	**Number of Complications**	**Complications per patient-year**
Device Related				
Infection	3	2.26%	7	0.07
Device migration	4	3.01%	4	0.04
Elective replacement indicator reached	4	3.01%	4	0.04
Inductions and conversions	1	0.75%	1	0.01
Unable to interrogate device	1	0.75%	1	0.01
Total	**12**	**9.02%**	**17**	**0.17**
Total Procedure and Device Related	**43**	**32.33%**	**58**	**0.57**
Other Medical Related				
Non-CHF Cardiac Symptoms	4	3.01%	4	0.04
Ventricular arrhythmias	2	1.50%	3	0.03
Other medical	2	1.50%	2	0.02
Atrial arrhythmia	1	0.75%	1	0.01
Total	**9**	**6.77%**	**10**	**0.10**
Total – All Patients and Categories	**50**	**37.59%**	**68**	**0.67**

Number of Patients = 133, Number of Patient-Years = 101.9

* 1 Unanticipated Adverse Device Effect (UADE) occurred with a Tupos LV/ATx CRT-D during the OPTION clinical study. The device was explanted after it was unable to be interrogated with the programmer software and no pacing output was evident. The analysis showed an appropriately depleted battery and no anomalies with the IC module. The battery depletion strongly suggests that the high voltage circuit was activated over a prolonged period due to a single-bit execution path failure. The current programmer software with Automatic Battery Management (ABM) would have prevented the battery from becoming completely depleted. There were no other instances of this failure mechanism in Tupos LV/ATx devices.

For the Tupos LV/ATx study group, there were 210 observations in 104 patients with cumulative implant duration of 1240.4 months (101.9 patient years). 78.2% of the enrolled study patients have a reported observation. The rate of observations per patient-year was 2.06. Table 4 summarizes by category each type of observation for the study group.

Table 4: Summary of Observations – Tupos LV/ATx

Category	Number of Patients	% of Patients	Number	per patient-year
Procedure Related				
Hematoma	10	7.52%	10	0.10
Cardiac arrest	2	1.50%	2	0.02
Unable to implant system	1	0.75%	1	0.01
Total	**13**	**9.77%**	**13**	**0.13**
Atrial Lead Related				
Dislodgement	1	0.75%	1	0.01
High threshold	1	0.75%	1	0.01
Total	**2**	**1.50%**	**2**	**0.02**
ICD Lead Related				
High threshold/No capture	1	0.75%	1	0.01
Total	**1**	**0.75%**	**1**	**0.01**
LV Lead Related				
High threshold/ Intermittent biventricular capture/ No capture	24	18.05%	24	0.24
Diaphragmatic/ Intercostal stimulation	8	6.02%	8	0.08
Total	**30**	**22.56%**	**32**	**0.31**

Table 4: Summary of Observations – Tupos LV/ATx				
Category	**Number of Patients**	**% of Patients**	**Number**	**per patient-year**
Device Related				
Infection	1	0.75%	1	0.01
Inductions and conversions	6	4.51%	6	0.06
Inappropriate sensing	20	15.04%	20	0.20
Symptomatic with biventricular pacing	2	1.50%	2	0.02
Total	**25**	**18.80%**	**29**	**0.28**
Total Procedure, Lead and Device Related	**61**	**45.86%**	**77**	**0.76**
Other Medical Related				
Non-CHF Cardiac Symptoms	21	15.79%	21	0.21
Ventricular arrhythmias	11	8.27%	11	0.11
Other medical	26	19.55%	32	0.31
Atrial arrhythmia	14	10.53%	14	0.14
Dizziness	4	3.01%	4	0.04
Medication	5	3.76%	5	0.05
Worsening CHF	46	34.59%	46	0.45
Total	**82**	**61.65%**	**133**	**1.31**
Total – All Patients and Categories	**104**	**78.20%**	**210**	**2.06**

Number of Patients = 133 Number of Patient-Years = 101.9

There have been 4 patient deaths reported for the control group (out of 67 total control patients) and 10 patient deaths have been reported for the study group (out of 133 total study patients). None of the deaths were related to the implanted CRT-D system. One patient in the control group died prior to receiving a biventricular device implant. There is no significant difference between the number of deaths in the study group versus the control group (p = 0.777, Fisher's Exact Test, 2 sided). Table 5 provides a summary of reported patient deaths and Table 6 provides survival percentages by follow-up interval during the first 12 months of study participation.

Table 5: Summary of Patient Deaths

Category of Death	Study (N = 133)	Control (N = 67)
	Number of Patients	Number of Patients
Sudden Cardiac	1	1
Non-Sudden Cardiac	5	2
Non-Cardiac	4	1
All Causes	10	4

Figure 1 shows the associated Kaplan-Meier survival curves for the study and control group. The significance level for the difference between the two study groups based on a Log Rank test was p = 0.795.

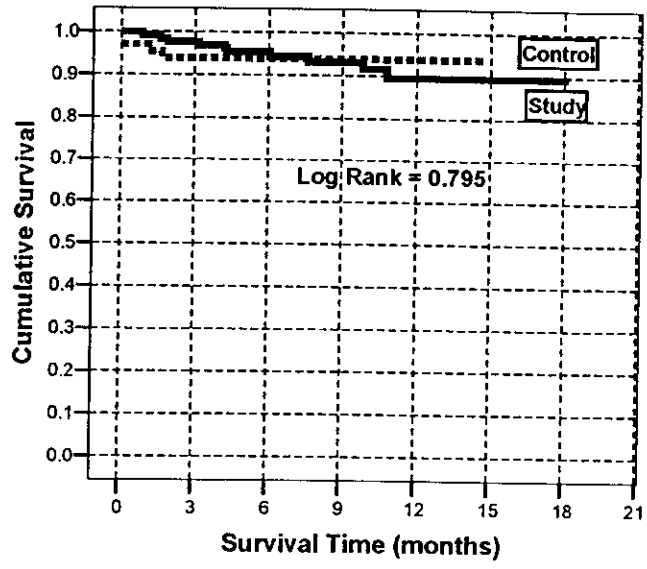


Figure 1: Kaplan-Meier Survival Curves

Table 6 Survival Table

	Study Group (n = 133)		Control Group (n = 66)	
	Number	%	Number	%
Enrollment	133	100.00%	67	100.00%
3-month	131	98.50%	63	94.03%
6-month	127	95.49%	63	94.03%
12-month	123	92.48%	63	94.03%

1.6 Clinical Studies

The Kronos LV Clinical study (HOME-CARE, Section 1.6.1) demonstrated the safety of the Kronos LV-T CRT-D device. Additionally, because the Tupos LV/ATx and the Kronos LV-T have identical CRT and ventricular ICD therapy, the effectiveness results from the OPTION CRT/ATx IDE Clinical study (Tupos LV/ATx, Section 1.6.2) support the effectiveness of the Kronos LV-T CRT-D.

1.6.1 Kronos LV-T Study

The purpose of the HOME-CARE Observational Study is to demonstrate the safety of the CE-marked Kronos LV-T cardiac resynchronization defibrillator (CRT-D) in patients with congestive heart failure (CHF).

1.6.1.1 Methods

The multi-center, non-randomized observational study was designed to evaluate the safety of the Kronos LV-T through an analysis of the complication-free rate through three months.

The Home-CARE Observational Study Primary Endpoint was to evaluate complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Kronos LV-T, the right atrial lead, the right ventricular ICD lead, and the left ventricular lead

Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Indication for Cardiac Resynchronization Therapy
- Sufficient GSM-network coverage in the patient's area
- Age greater than or equal to 18 years

Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Permanent atrial fibrillation
- Myocardial infarction or unstable angina pectoris within the last 3 prior to enrollment
- Planned cardio-surgical intervention within 3 months after enrollment (e.g. PTCA, CABG, HTX)
- Acute myocarditis
- Life expectancy less than 6 months
- Pregnant or breast-feeding woman
- Drug or Alcohol abuse
- The patient is mentally or physically unable to take part in the observational study
- No signed declaration of consent for the patient

At the enrollment screening, the physician evaluated the patient to verify that all inclusion/exclusion criteria were met in accordance to the protocol and the patient signed the informed consent. After successful enrollment, all patients were implanted with the Kronos LV-T CRT-D. Evaluations at the One- and Three-month follow-ups included resting ECG, NYHA classification, medications, and activation of Home Monitoring.

1.6.1.2 Summary of Clinical Results

The study involved 45 patients (37 males, 82.2%, and 8 females, 17.8%), with a mean age of 64 years (range: 36-79), a left ventricular ejection fraction of 26 % (range: 15-43), NYHA Class III (NHYA Class 1 (2.3%), Class II (11.4%), Class III (79.5%), Class IV (6.8%)) and QRS duration of 154 ms (range: 84-208).

The mean implant duration was 4.5 months with a cumulative implant duration of 202 months. The patient follow-up compliance rate was 95.9% out of 221 required follow-ups.

Primary Endpoint

The safety of the Kronos LV-T was evaluated based on complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Kronos LV-T, the right atrial lead, the right ventricular ICD lead, and the left ventricular lead. 5 complications were seen in 3 patients with cumulative implant duration of 202 months (16.8 patient-years). 6.7% of the patients had a reported complication. The rate of complications per patient-year is 0.30.

The freedom from Kronos LV-T system-related complications is 93.3% with a two sided lower 95% confidence bound of 83.8%. The null hypothesis is rejected, and it is concluded that the complication-free rate is equivalent to 85% within 10%.

1.6.2 Tupos LV/ATx Study

NOTE:

The clinical study information included in this section was performed with the Tupos LV/ATx CRT-D, which is an earlier version of the Kronos LV-T CRT-D. The clinical study data presented here is applicable because the Kronos LV-T is a downsized version of the Tupos LV/ATx. The Kronos LV-T CRT-D is slightly different as compared to the Tupos LV/ATx in the following areas:

- Reduced size from 48 cc to 41 cc
- Addition of Home Monitoring functionality
- Addition of triggered pacing for biventricular pacing modes

1.6.2.1 Study Overview

The purpose of the prospective, randomized, multi-center OPTION CRT/ATx study was to demonstrate the safety and effectiveness of the investigational Tupos LV/ATx Cardiac Resynchronization Therapy Defibrillator (CRT-D) in patients with congestive heart failure (CHF) and atrial tachyarrhythmias. Patients in the study group were implanted with a BIOTRONIK Tupos LV/ATx. Patients in the control group were implanted with any legally marketed CRT-D. Patients in both the study and

control groups were implanted with a legally marketed left ventricular lead.

1.6.2.2 Methods

Primarily, the study evaluates and compares the functional benefits of CRT between the two randomized groups using a composite endpoint consisting of a six-minute walk test (meters walked) and quality of life measurement (assessed using the Minnesota Living with Heart Failure Questionnaire). Relevant measurements were completed twice for each patient: once at the Baseline evaluation (two-week post implant follow-up) and again at a six-month follow-up evaluation. The data collected during this clinical study was used to demonstrate equivalent treatment of CHF in both the study and control groups. This study also evaluated other outcomes including: the effectiveness of atrial therapy to automatically convert atrial tachyarrhythmias, the percentage of time CRT is delivered, and other measures of CHF status including NYHA classification, peak oxygen consumption during metabolic exercise testing, and the rate of hospitalization for CHF.

Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Stable, symptomatic CHF status
- NYHA Class III or IV congestive heart failure
- Left ventricular ejection fraction ≤ 35% (measured within Six-Months prior to enrollment)
- Intraventricular conduction delay (QRS duration greater than or equal to 130 ms)
- For patients with an existing ICD, optimal and stable CHF drug regimen including ACE-inhibitors and beta-blockers unless contraindicated (stable is defined as changes in dosages less than 50% during the last 30 days)
- Indicated for ICD therapy
- History or significant risk of atrial tachyarrhythmias
- Willing to receive possibly uncomfortable atrial shock therapy for the treatment of atrial tachyarrhythmias

- Able to understand the nature of the study and give informed consent
- Ability to tolerate the surgical procedure required for implantation
- Ability to complete all required testing including the six-minute walk test and cardiopulmonary exercise testing
- Available for follow-up visits on a regular basis at the investigational site
- Age greater than or equal to 18 years

Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Previously implanted CRT device
- ACC/AHA/NASPE indication for bradycardia pacing (sinus node dysfunction)
- Six-minute walk test distance greater than 450 meters
- Chronic atrial tachyarrhythmias refractory to cardioversion shock therapy
- Receiving intermittent, unstable intravenous inotropic drug therapy (patients on stable doses of positive inotropic outpatient therapy for at least One-Month are permitted)
- Enrolled in another cardiovascular or pharmacological clinical investigation
- Expected to receive a heart transplant within 6 months
- Life expectancy less than 6 months
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Acute myocardial infarction, unstable angina or cardiac revascularization within the last 30 days prior to enrollment
- Conditions that prohibit placement of any of the lead systems

1.6.2.3 Summary of Clinical Results

A total of 200 patients were enrolled in the OPTION CRT/ATx clinical study at 25 sites:

There were 133 study patients and 67 active control patients in this prospective, multi-center, randomized clinical study. For the study group, there were 129 successful implants (91.4%) of the Tupos LV/ATx CRT-D system. For the active control group, there were 64 successful implants (92.2%) of the legally marketed CRT-D systems.

Patient Accountability

After randomization and enrollment, 7 patients (4 in the study group and 3 in the control group) did not receive an implant. The reasons for patients not receiving an implant are outlined in Figure 2.

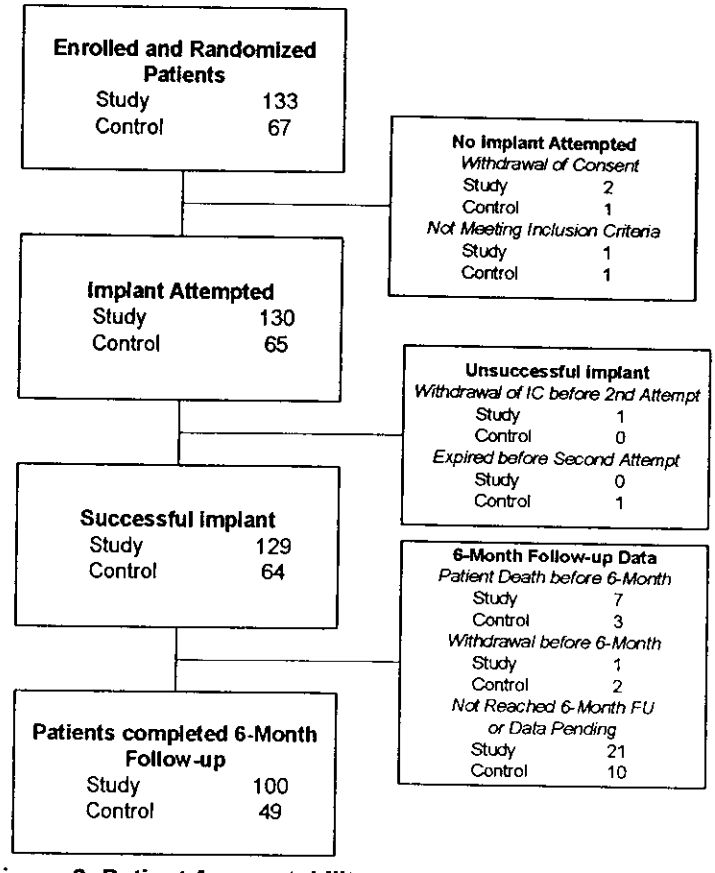


Figure 2: Patient Accountability

Overall Results

- There were 192 endocardial and 19 epicardial leads implanted in 193 patients. Investigators were allowed to choose among any legally marketed LV lead according to familiarity with the lead and patient anatomy. The Tupos LV/ATx CRT-D was implanted with 7 endocardial and 4 epicardial lead models from 6 different manufacturers. There were no adverse events reported attributable to lead-generator incompatibility.

- The cumulative implant duration was 1240.4 months with a mean duration of 9.6 months for the study group. The cumulative implant duration is 596.5 months with a mean duration of 9.3 months for the control group.
- For the study group, there have been 278 adverse events (210 observations in 104 patients and 68 complications in 50 patients). There has been one unanticipated adverse device effect reported.
- For the control group, there have been 105 adverse events (81 observations in 44 patients and 24 complications in 19 patients). There have been no unanticipated adverse device effects reported.
- There have been 10 patient deaths reported in the study group and 4 patient deaths reported in the control group. The clinical investigators have determined that no deaths were related to the study device.

1.6.2.4 Primary Endpoint 1: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 is to evaluate the effectiveness of the Tupos LV/ATx system in providing CRT as measured by the average composite rate of improvement in six minute walk test and QOL.

Table 7 presents the average composite rate of improvement in six minute walk test distance and QOL score, the average 6-minute walk test distance and the average QOL score at Baseline and at the Six-Month follow-up, as well as the average difference in 6-minute walk test distance and QOL score between Baseline and the Six-Month follow-up for the Study and Control Groups for those patients with six minute walk test data and complete QOL data at both Baseline and the Six-Month follow-up.

Table 7: Composite of Six Minute Walk Test and QOL (Effectiveness)

Category	Study Group (N = 74) Mean ± SE	Control Group (N = 38) Mean ± SE	P-value*
Distance Walked at Baseline	310.51 ± 10.89	288.76 ± 15.37	0.249
Distance Walked at Six-Months	340.77 ± 12.32	301.84 ± 17.02	0.067
Δ Distance Walked	30.26 ± 10.40 17.27% ± 5.59%	13.08 ± 13.05 8.71% ± 5.26%	0.322 0.326
QOL Score at Baseline	44.39 ± 2.78	45.53 ± 4.13	0.817
QOL Score at Six-Months	28.68 ± 2.66	33.95 ± 4.35	0.279
Δ in QOL Score**	15.72± 2.83 19.08% ± 12.21%	11.58 ± 3.45 -13.42% ± 34.54%	0.376 0.281
Composite Rate***	18.18% ± 7.07%	-2.36% ± 17.73%	0.030

*The calculated p-values are associated with a Student's t-test (2-sided) of the equality of means in the two groups, except for the p-value of the composite rate, which is associated with a test of equivalence (non-inferiority).

**Δ in QOL Score is calculated as the average of the individual differences between Baseline and Six-Months for each patient. Negative values for mean Δ QOL in percent are possible when positive mean values for absolute changes in QOL are recorded. In some cases, small, negative changes in absolute QOL scores resulted in relatively large percentage changes.

***The Composite Rate (=(Δ Distance Walked (%) + Δ QOL Score (%)) / 2) is calculated for each patient and then averaged to obtain the Composite Rates. For all calculations, a positive number represents improvement from Baseline to Six-Months.

1.6.2.5 Effectiveness Endpoint Analysis and Conclusions

A composite rate of six minute walk test and QOL improvement from Baseline to the Six-Month follow-up is evaluated as a measure of CRT effectiveness. For this analysis both six minute walk test and QOL are equally weighted at 50%.

The mean difference in the composite rate between study and control group was 20.53% with an associated one-sided, 95% confidence bound is (-6.10%). The p-value for non-inferiority within 10% is 0.030. The analysis of the composite rate in six minute walk test distance and QOL score demonstrates that the study group is non-inferior to the control group and that the primary effectiveness endpoint was met (p=0.030).

1.6.2.6 Primary Endpoint 2: Complication-Free Rate (Safety)

The purpose of Primary Endpoint 2 was to evaluate complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Tupos LV/ATx, the right atrial lead, the right ventricular ICD lead, the left ventricular lead, and the implant procedure. The target complication-free rate at Six-Months is 85%.

Table 8 provides the categorized complication rates at 6-months for the study and the control group as well as a comparison between the study and the control group.

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Table 8: Complications at 6-Month – Study and Control					
Category	Study N = 133	Control N = 67	Study versus Control Comparison		
			Delta	95% CI	P-value
Procedure Related	6 (4.51%)	1 (1.49%)	3.02 %	[-3.64%, 8.45%]	0.428
Atrial Lead Related	3 (2.26%)	1 (1.49%)	0.76 %	[-5.74%, 5.37%]	1.000
ICD Lead Related	3 (2.26%)	0 (0%)	2.26 %	[-3.03%, 6.53%]	0.552
LV Lead Related	26 (19.55%)	9 (13.43%)	6.12 %	[-5.50%, 16.45%]	0.329
Device Related	7 (5.26%)	5 (7.46%)	- 2.20 %	[-11.42%, 4.77%]	0.541
Other Medical Related	9 (6.77%)	2 (2.99%)	3.78 %	[-3.82%, 10.13%]	0.341
Total Procedure, Lead and Device Related	39 (29.32%)	15 (22.39%)	6.94 %	[-6.46%, 19.17%]	0.317
Total	**46 (34.59%)**	**17 (25.37%)**	**9.21 %**	**[-4.96%, 21.99%]**	**0.201**

1.6.2.7 Primary Safety Enpoint Analysis and Conclusions

The observed procedure, lead and device related complication-free rate at 6 months was 70.68%. The 95% confidence interval for the complication-free rate was [62.16%, 78.25%]. The lower, one-sided 95% confidence bound for the complication-free rate was 63.50%. Therefore the procedure, lead and device related complication-free rate at 6 months did not meet the pre-specified acceptance criterion for this endpoint.

1.6.2.8 Post-hoc Safety Analysis

BIOTRONIK did not meet the pre-specified objective performance criteria of 85% within 10% for the safety endpoint. Therefore, a post-hoc safety analysis was conducted. It was noted that 79.80% (39 out of 49 events) of the complications were right atrial lead, right ventricular ICD lead, left ventricular lead and procedure related. The atrial, ICD and LV leads used during this study are legally marketed devices.

This post-hoc analysis evaluated the LV lead complications that were "related" or "possibly related" to the Tupos LV/ATx CRT-D, but excludes the complications that were "not related" to the Tupos LV/ATx device (see Table 9). There were 11 patients who had an attempt to implant the LV lead, but the physician was unsuccessful in either obtaining coronary sinus (CS) access or unable to find a stable position for the LV lead. Additionally, there were 4 patients with a documented LV lead dislodgement that has no direct relationship to the implanted Tupos LV/ATx.

Table 9: Complications at 6-Months (Excluding LV Lead Related) - Study versus Control

Category	Study N=133	Control N=67	Difference Study vs Control
Procedure Related	6 (4.51%)	2 (2.99%)	1.53%
Atrial Lead Related	3 (2.26%)	1 (1.49%)	0.76%
ICD Lead Related	3 (2.26%)	0 (0%)	2.26%
LV Lead Related	11 (8.27%)	1 (1.49%)	6.78%
Device Related	7 (5.26%)	5 (7.46%)	-2.20%
Other Medical Related	9 (6.77%)	2 (2.99%)	3.78%
Total Procedure, Lead and Device Related	27 (20.30%)	8 (11.94%)	8.36%
Total	**35 (26.32%)**	**10 (14.93%)**	**11.39%**

The pulse generator related complication rate is higher in the control group as compared to the study group. The complication rates for procedure related, atrial lead related, ICD lead related, LV lead related and other medical related are higher in the study group as compared to the control group.

1.6.2.9 Post hoc Safety Analysis Conclusion

There are no clinically substantial differences in the total complication rate or in the rates for the different complication rate categories between the study and the control group.

Table 10 compares this post-hoc Safety Endpoint analysis to previous CRT-D clinical studies:

Table 10 Safety Endpoint Comparisons

CRT-D Study	Estimated freedom from Complications @ 6mos.	Lower 95% CI	95% lower bound criteria
BIOTRONIK OPTION (Original Analysis)	70.68%	63.5%	75%
BIOTRONIK OPTION (Post-hoc Analysis)	78.95%	72.29%	75%
Medtronic Insync ICD	81.1%	77.6%	67%
Guidant Contak CD	N/A	N/A	70%
St. Jude Medical Epic HF	93.4%	90.6%	70%

This analysis confirms that the safety profile of the Tupos LV/ATx is within a similar range determined during trials of other legally marketed CRT-D devices.

1.6.2.10 Secondary Endpoint Results

1. The purpose of Secondary Endpoint 1 is to evaluate the overall ability of the Tupos LV/ATx to appropriately convert spontaneous AT (atrial tachycardia) and AF (atrial fibrillation). The results from the OPTION study were compared to the results from BIOTRONIK's TACT study (P000009/S4, dated 09-09-2002) that demonstrated the effectiveness of these atrial therapy features in the Tachos DR - Atrial Tx ICD.

   Table 11 summarizes success rates for each individual atrial tachyarrhythmia therapy type and overall success rate from the OPTION study compared to the TACT study. The number of episodes and patients receiving any therapy is less than the total episodes of each therapy type, as episodes may have included more than one type of therapy.

Table 11 Overall Atrial Conversion Rate

Patients	OPTION Study			
	Patients	Success	Episodes	Conversion rate
ATP	3	3	5	60.0%
HF Burst	17	45	111	40.5%
Shock	12	30	34	88.2%
All Therapies	**25**	**78**	**129**	**60.5%**
TACT Study				
ATP	29	62	142	43.6 %
HF Burst	49	156	408	38.2 %
Shock	42	84	108	77.8 %
All Therapies	**66**	**302**	**542**	**55.7 %**

   The overall conversion rate and the conversion rates for each therapy are comparable to the conversion rates observed in the TACT study, demonstrating that the Tupos LV/ATx device has similar atrial conversion capabilities as the legally marketed Tachos DR – Atrial Tx ICD.

2. The purpose of Secondary Endpoint 2 is to evaluate VT (ventricular tachycardia) and VF (ventricular fibrillation) detection times of the Tupos LV/ATx. This is a measure of

the ability of the ventricular detection algorithm to detect VT and VF in an appropriate timeframe. This endpoint was evaluated based on the review of electrograms following induced VT/VF episodes. A comparison of data from the TACT study that utilized the legally marketed Tachos DR – Atrial Tx ICD (P000009/S4, dated 09-09-2002) to data collected during the OPTION study for the Tupos LV/ATx was performed.

Table 12 summarizes and compares the results from these two clinical studies.

Table 12: Summary of Detection Times

Detection Time	Tachos DR - Atrial Tx ICD Mean (SE) / N	Tupos LV/ATx Mean (SE) / N	Difference
Individual Readings	2.27 (0.06) / 52	2.26 (0.06) / 71	0.01
By Patient	2.27 (0.07) / 26	2.24 (0.06) / 35	0.03

The analysis demonstrates that the average detection times of the Tupos LV/ATx are comparable to the detection times observed with the legally marketed Tachos DR - Atrial Tx ICD. Both devices utilize identical ventricular detection algorithms and only sense with the right ventricular lead. This clinical data demonstrates that the ventricular detection times are similar in both devices.

3. The purpose of Secondary Endpoint 3 is to evaluate the percentage of ventricular pacing (thus, CRT) as demonstrated by the device diagnostics at required follow-ups. This data was based on diagnostic data stored by the Tupos LV/ATx.

   Table 13 summarizes the percentage of ventricular pacing between follow-ups as shown by device diagnostics for patients in the study group.

Table 13: Percentage of Ventricular Pacing – 3-Month and 6-Month Follow-ups

Percentage of Ventricular Pacing	3-Months Patients (percentage)	6-Months Patients (percentage)
<80%	9 (7.4%)	4 (4.0%)
81 – 85 %	4 (3.3%)	2 (2.0%)
86 – 90 %	13 (10.7%)	9 (9.1%)
91 – 95 %	19 (15.7%)	20 (20.2%)
96 – 100 %	76 (62.8%)	64 (64.7%)
Totals	**121 (100%)**	**99 (100%)**

The majority of the follow-ups (84.9%) show a percentage of ventricular pacing of 91% or more at Six-Months.

4. The purpose of secondary endpoint 4 is to evaluate improvement in functional capacity as measured by the six minute walk test. The six minute walk test is a well-accepted measure of functional capacity and exercise tolerance. Also, this test more closely mimics the patient's day-to-day activities than maximal exercise testing.

   Table 14 summarizes the six minute walk test distance at Baseline and the Six-Month follow-up for patients in the study group and the control group.

Table 14: Six Minute Walk Distance

Distance (meters)	Study	Control
Baseline		
N	127	61
Mean ± SE	283.14 ± 9.27	269.43 ± 13.77
Range	23 to 511	29 to 507
Median	302.00	244.00
Six-Month		
N	93	44
Mean ± SE	329.73 ± 10.82	310.70 ± 15.49
Range	78 to 596	91 to 489
Median	335.00	313.00

* Student's t-test, 2-sided

There are no clinically relevant differences in the six minute walk test results between the study and the control group.

5. The purpose of Secondary Endpoint 5 is to evaluate the improvement in the patient's NYHA classification. Table 15 summarizes the average improvement in NYHA from Baseline to Six-Months for 140 patients that were able to complete both NYHA classification evaluations.

Table 15: Improvement in NYHA Classification at Six-Months from Baseline

NYHA Change During OPTION Study		
Change in NYHA Class	Study Patients (N=97) (percentage)	Control Patients (N=43) (percentage)
Improved 2 classes	10 (10.3%)	2 (4.7%)
Improved 1 class	47 (48.5%)	20 (46.5%)
Total improved	57 (58.8%)	23 (51.2%)
No change	39 (40.2%)	20 (46.5%)
Worsened 1 class	1 (1.0%)	1 (2.3%)

The study and the control group have similar NYHA classes and similar rates of improvement in NYHA class from Baseline to the Six-Month follow-up.

6. The purpose of Secondary Endpoint 6 is to evaluate the rate of hospitalization, for CHF and for all other causes. The occurrence rate and reasons for hospitalization of the study group were compared to the control group. To be consistent with other large-scale clinical trials, clinical sites were instructed to report hospitalizations for CHF using the following definitions: 1) hospitalization for heart failure management, 2) outpatient visit in which IV inotropes or vasoactive infusion are administered continuously for at least 4 hours, or 3) emergency room (ER) visit of at least 12 hours duration in which intravenous heart failure medications including diuretics are administered.

Table 16 summarizes hospitalization, ER visits and outpatient visits for enrolled patients.

Table 16: Hospitalization, ER Visits and Outpatient Visits

Medical Visits	Study (N=128)	Control (N=65)
Hospital Admissions	**CHF Related:**	**CHF Related:**
Patients	20 (15.6%)	5 (7.7%)
Hospitalizations	28	9
	All causes:	All causes:
Patients	68 (53.1%)	29 (44.6%)
Hospitalizations	76	46
Emergency Room Visits	**CHF Related:**	**CHF Related:**
Patients	1 (0.8%)	0 (0.0%)
Visits	1	0
	All causes:	All causes:
Patients	13 (10.1%)	2 (3.1%)
Visits	16	2
Outpatient Visits		
Patients	**CHF Related:**	**CHF Related:**
Visits	1 (0.8%)	0 (0.0%)
	1	0
Patients	All causes:	All causes:
Visits	5 (3.9%)	2 (3.1%)
	5	2

A large percentage of All Cause hospitalizations can be attributed to pacing lead revisions, device infections, or other device-related interventions (e.g., pocket revision or device replacements for ERI or device recall). The CHF hospitalization rate for both the study and control groups is clinically acceptable considering the enrollment CHF status of the patients.

7. The purpose of Secondary Endpoint 7 is to evaluate the observation rate. Observations are defined as clinical events that do not require additional invasive intervention to resolve. For the study group, there were 210 observations in 104

patients with cumulative implant duration of 1240.4 months (101.9 patient years). 78.2% of the enrolled study patients have a reported observation. The rate of observations per patient-year is 2.06. For the control group, there were 81 observations in 44 patients with cumulative implant duration of 596.5 months (49.0 patient years). 65.7% of the enrolled control patients had a reported observation. The rate of observations per patient-year was 1.65.

8. The purpose of Secondary Endpoint 8 is to evaluate peak VO2 as a measure of effectiveness of the Tupos LV/ATx system in providing CRT. The core lab was blinded to study randomization assignments during evaluation of the results of the cardiopulmonary exercise (CPX) testing in order to minimize the potential for bias. According to the protocol, to be included in the analysis, patients were required to attain a respiratory exchange ratio (RER) of ≥ 1.

   Table 17 provides a summary of peak VO_2 results for 42 patients with CPX testing completed at Baseline and the Six-Month follow-up and with an RER of ≥ 1.

Table 17: Peak VO2 Testing Results – Patients with RER ≥ 1

Results	Study	Control
Peak VO_2 (ml/kg/min)	**N=32** **Baseline:** Mean: 13.46 ± 0.57 Range: 6.9 to 21.1 **Six-Month:** Mean: 13.39 ± 0.53 Range: 7.6 to 20.70 **Difference:** Mean: -0.06 ± 0.42 Range: -7.9 to 4.9	**N=10** **Baseline:** Mean: 12.58 ± 0.75 Range: 8.0 to 14.8 **Six-Month:** Mean: 12.89 ± 0.94 Range: 7.0 to 17.2 **Difference:** Mean: 0.31 ± 0.67 Range: -2.7 to 4.6

1.6.2.11 Multi-site Poolability and Gender Analysis

The OPTION CRT/ATx clinical report includes data from multiple centers with centralized coordination, data processing, and reporting at BIOTRONIK. All of the clinical centers followed the requirements of an identical clinical protocol, and all of the clinical centers used the same methods to collect and report the clinical data. In order to justify pooling of the data from multiple centers, several analyses were completed. All of the centers were divided into two groups based on implant volume. Comparisons were then made between the patient populations based on the results of each of the endpoints. Additionally, analyses were performed on the data collected in the OPTION CRT/ATx clinical investigation in order to compare results between males and females. The first type of analysis compared enrollment by patient gender in each of the study and control groups. The second type of analysis compared effectiveness outcomes in each gender.

The results of these analyses demonstrate poolability of the data between sites. There were no significant differences in the second primary endpoint or any of the secondary endpoints between high and low volume implant centers.

The gender distribution in this clinical investigation is consistent within the study groups and includes a representative proportion of female participants. There were no significant differences in any of the primary or secondary endpoints between the male and female population.

1.6.2.12 Conclusions

The IDE Clinical study (OPTION LV/ATx) demonstrated that the safety and effectiveness of the Tupos LV/ATx CRT-ICD device is equivalent to that of similar legally marketed CRT-D devices. Although the study missed its primary safety endpoint, additional post hoc analyses were conducted to reassure that the safety profile of the device is comparable to other legally marketed CRT-D devices.

1.7 Patient Selection and Treatment

1.7.1 Individualization of Treatment

- Determine whether the expected device benefits outweigh the possibility of early device replacement for patients whose biventricular pacing thresholds are very high.
- Determine if the device and programmable options are appropriate for patients with drug-resistant supraventricular tachyarrhythmias (SVTs), because drug-resistant SVTs can initiate unwanted device therapy.
- Direct any questions regarding individualization of patient therapy to your BIOTRONIK representative or BIOTRONIK technical services at 1-800-547-0394.

The prospective patient's size and activity level should be evaluated to determine whether a pectoral or abdominal implant is suitable. It is recommended that candidates for a CRT-D have a complete cardiac evaluation including EP testing prior to device implant to gather electrophysiologic information, including the rates and classifications of all the patient's cardiac rhythms. When gathering this information, delineate all clinically significant ventricular and atrial arrhythmias, whether they occur spontaneously or during EP testing.

If the patient's condition permits, use exercise stress testing to do the following:

- Determine the maximum rate of the patient's normal rhythm.
- Identify any supraventricular tachyarrhythmias.
- Identify exercise-induced tachyarrhythmias.

The maximum exercise rate or the presence of supraventricular tachyarrhythmias may influence selection of programmable parameters. Holter monitoring or other extended ECG monitoring also may be helpful.

If the patient is being treated with antiarrhythmic or cardiac drugs, the patient should be on a maintenance drug dose rather than a loading dose at the time of pulse generator implantation. If changes to drug therapy are made, repeated pacing threshold testing and arrhythmia inductions are recommended to verify CRT-D treatment, detection and conversion. The CRT-D also may need to be reprogrammed.

Changes in a patient's antiarrhythmic drug or any other medication that affect the patient's normal cardiac rate or conduction can affect the rate of tachyarrhythmias and/or efficacy of therapy.

If another cardiac surgical procedure is performed prior to implanting the pulse generator, it may be preferable to implant the lead system at that time. This may prevent the need for an additional thoracic operation.

1.7.2 Specific Patient Populations

Pregnancy - If there is a need to image the device, care should be taken to minimize radiation exposure to the fetus and the mother.

Nursing Mothers - Although appropriate biocompatibility testing has been conducted for this implant device, there has been no quantitative assessment of the presence of leachables in breast milk.

Geriatric Patients - Most (71%) of the patients receiving a CRT-D in the Kronos clinical study were over the age of 60 years (see Clinical Studies).

Handicapped and Disabled Patients - Special care is needed in using this device for patients using electrical wheel chair or other electrical (external or implanted devices).

1.8 Patient Counseling Information

The pulse generator is subject to random component failure. Such failure could cause inappropriate shocks, induction of arrhythmias or inability to sense arrhythmias, and could lead to the patient's death.

Persons administering CPR may experience the presence of voltage on the patient's body surface (tingling) when the patient's CRT-D system delivers a shock.

A patient manual is available for the patient, patient's relatives, and other interested people. Discuss the information in the manual with concerned individuals both before and after pulse generator implantation so they are fully familiar with operation of the device. (For additional copies of the patient manual, contact the BIOTRONIK at the address listed in this manual.)

1.9 Evaluating Prospective CRT-D Patients

The prospective CRT-D implant candidate should undergo a cardiac evaluation to classify any and all tachyarrhythmias. In addition, other patient specific cardiac information will help in selecting the optimal device settings. This evaluation may include, but is not limited to:

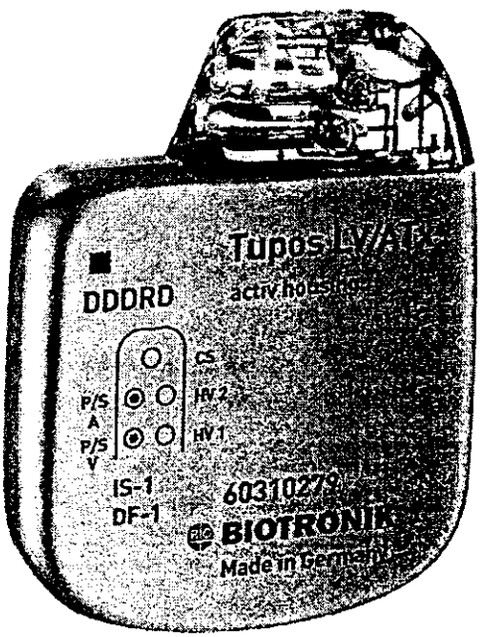
- an evaluation of their heart failure status
- an evaluation of the specific tachycardia rate(s)
- the confirmation and/or evaluation of any supraventricular arrhythmias or bradyarrhythmias
- the evaluation of various ATP and cardioversion therapies
- the presence of any post-shock arrhythmias, and
- an evaluation of the maximum sinus rate during exercise

If a patient's drug regimen is changed or adjusted while the CRT-D is implanted, additional EP testing may be required to determine if detection or therapy parameter settings are relevant and appropriate.

Empirical changes to the detection or therapy parameters should be assessed based on patient safety. Some changes may necessitate a re-assessment of sensing, pacing, or arrhythmia conversion treatment. Thorough technical knowledge of BIOTRONIK CRT-Ds, additional CRT-D experience, and individual medical judgment will aid in determining the need for additional testing and follow-up.

Tupos LV/ATx

Cardiac Resynchronization Therapy - Defibrillator

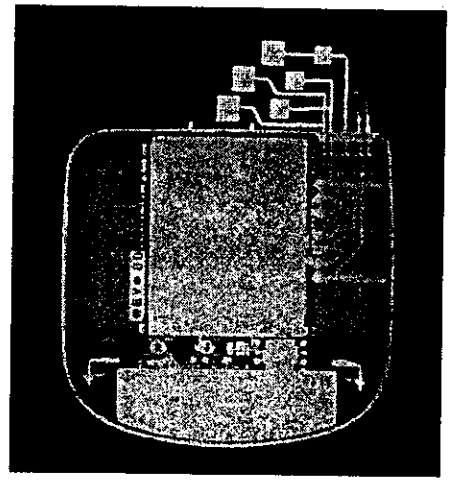


Technical Manual

BIOTRONIK

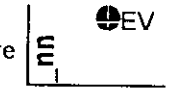
Tupos LV/ATx Cardiac Resynchronization Therapy - Defibrillator

X-ray Identification



Inside the housing, top right-hand side:

x-ray identification
Year of manufacture



CAUTION

Federal (U.S.A.) law restricts this device to sale by, or on the order of, a physician.

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Tupos LV/ATx Specifications

Model:	335 870
1st Battery Voltage:	6.3 Volts
2nd Battery Voltage:	2.8 Volts
Maximum Shock Energy:	30 Joules
Defibrillation Lead Ports	Two DF-1 (3.2 mm)
Pacing Lead Ports	Three IS-1 (3.2 mm)
Dimension:	72 x 57 x 15 mm
Volume:	50 cc
Mass:	108 g

Tupos LV/ATx Description

Housing Material:	Titanium
Header Material:	Epoxy Resin
Sealing Plug Material:	Silicone
1st Battery Material	Li / MnO_2
2nd Battery Material	Li / I

CAUTION

Federal (U.S.A.) law restricts this device to sale by, or on the order of, a physician.

1. General

1.1 System Description

Some patients with congestive heart failure also have an intraventricular conduction delay that results in unsynchronized contractions of the heart. The Tupos LV/ATx is a Cardiac Resynchronization Therapy - Defibrillator (CRT-D) designed to provide Cardiac Resynchronization Therapy. This Tupos LV/ATx Cardiac Resynchronization Therapy (CRT) system includes an ICD (Implantable Cardioverter Defibrillator), with pacing leads for left ventricular stimulation, atrial sensing/pacing lead and an ICD lead. Together, this system provides therapy to convert VT/VF and treat congestive heart failure. The Tupos LV/ATx may be implanted with any legally marketed ICD lead.

The Tupos LV/ATx CRT-D provides biventricular pacing through a fifth header port (CS port in previous figure) utilizing an IS-1 unipolar connector for the left ventricular (LV) channel. The Kronos LV-T provides CRT in a "shared-ring" configuration with both the RV and LV outputs tied together and are only programmable to a single value for both outputs.

The five port header of the Tupos LV/ATx has three IS-1 connector ports for the right atrial lead, the right ventricular lead and the left ventricular lead, and two DF 1 connector ports for the ICD lead (if applicable). Bipolar IS-1 connectors are used for pacing and sensing the right atrium and ventricle. The IS-1 connection used for pacing in the left ventricle is a unipolar configuration.

As with all of BIOTRONIK's CRT-Ds, the Tupos LV/ATx uses the two DF-1 defibrillation/cardioversion ports for providing shock therapy in response to ventricular tachyarrhythmias.

The CRT-D uses atrial and ventricular sensing/pacing leads to provide enhanced atrial and ventricular tachyarrhythmia discrimination through BIOTRONIK's SMART Detection™ algorithm. Ventricular sensing of the Tupos LV/ATx lead is derived exclusively from the right ventricular lead. This is particularly important for the ability to detect ventricular fibrillation (VF), which are often times accompanied by a significant decrease in signal amplitude.

The CRT-D is also designed to collect diagnostic data to aid the physician's assessment of a patient's condition and the performance of the implanted device. The Tupos LV/ATx provides therapy for ventricular tachyarrhythmias with a sophisticated range of programmable antitachycardia pacing (ATP), and/or defibrillation therapy. The shock polarity and energy may be programmed to tailor the therapy to appropriately treat each patient's tachyarrhythmias. The CRT-D provides biphasic shocks with programmable energies from 1 to 30 joules.

The Tupos LV/ATx provides an additional feature named "Implant Assistant," as well as additional statistics for improved diagnostics. The Implant Assistant facilitates device programming during the implant procedure based on expert knowledge. The feature requires the physician to enter patient symptoms and data in clinically relevant terminology to establish a complete set of recommended and editable parameter settings.

External devices that interact with and test the implantable devices are also part of the CRT-D System. These external devices include the TMS 1000 PLUS Tachyarrhythmia Monitoring System and the EPR 1000 PLUS Programming and Monitoring System. These programmers are used to interrogate and program the CRT-D.

1.2 Indications and Usage

The Tupos LV/ATx is indicated for use in patients with all of the following conditions:

- Indicated for ICD therapy
- Receiving optimized and stable Congestive Heart Failure (CHF) drug therapy
- Symptomatic CHF (NYHA Class III/IV and LVEF ≤ 35%); and
- Intraventricular conduction delay (QRS duration ≥ 130 ms)

The Tupos LV/ATx is also indicated for patients who, in addition to an indication for a CRT-D device, have atrial tachyarrhythmias or are at risk of developing atrial tachyarrhythmias.

1.3 Contraindications

The Tupos LV/ATx is contraindicated for use in patients with the following conditions:

- Patients whose ventricular tachyarrhythmias may have transient or reversible causes such as:
  - Acute myocardial infarction
  - Digitalis intoxication
  - Drowning
  - Electrocution
  - Electrolyte imbalance
  - Hypoxia
  - Sepsis
- Patients with incessant ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Patients whose only disorder is bradyarrhythmias or atrial arrhythmias

1.4 Warnings and Precautions

MRI (Magnetic Resonance Imaging) - Do not expose a patient to MRI device scanning. Strong magnetic fields may damage the device and cause injury to the patient.

Electrical Isolation - To prevent inadvertent arrhythmia induction, electrically isolate the patient during the implant procedure from potentially hazardous leakage currents.

Lead Systems – BIOTRONIK CRT-Ds maybe implanted with any legally marketed, compatible ICD lead. Compatibility is defined as:

- IS-1 pacing and sensing connector(s)
- DF-1 shock coil connector(s)
- Integrated or dedicated bipolar pacing and sensing configuration
- Active or passive fixation technology
- Single or dual defibrillation shock coil (s)
- High energy shock accommodation of at least 30 joules
- Insertion and withdrawal forces as specified by ISO 5841-3 (IS-1) and ISO 11318:1993 (E) DF-1

The following leads were evaluated in a retrospective study with BIOTRONIK's ICDs:

- Medtronic Sprint 6932
- Medtronic Sprint 6943
- Medtronic Sprint Quattro 6944
- Medtronic Transvene RV 6936
- St. Jude (Ventritex) TVL- ADX 1559
- St. Jude SPL SP02
- Guidant Endotak DSP
- Guidant Endotak Endurance EZ, Endotak Reliance
- Guidant (Intermedics) 497-24.

The following leads were bench tested for compatibility with BIOTRONIK's ICDs:

- Guidant Endotak Endurance "CPI 0125"
- Guidant Endotak Reliance 0148
- Medtronic Sprint 6932
- Medtronic Sprint 6942
- Medtronic Sprint 6943
- Medtronic Sprint 6945
- Medtronic Sprint Quattro 6944
- St. Jude Riata 1571/65
- St. Jude SPL SPO1

Left Ventricular Lead Systems – BIOTRONIK CRT-Ds maybe implanted with any legally marketed, compatible LV lead. Compatibility is defined as:

- IS-1 pacing connector
- Active or passive fixation technology
- Insertion and withdrawal forces as specified by ISO 5841-3 (IS-1)

The following LV leads were evaluated in OPTION CRT/ATx study with BIOTRONIK's CRT-Ds:

- Guidant-Easytrak IS-1
- Guidant-Easytrak LV-1
- Guidant-Easytrak 2
- Guidant-Easytrak 3
- Medtronic-Attain
- St. Jude-Aescula
- St. Jude-Quicksite
- Biomec-Myopore Epicardial
- Medtronic-Epicardial 5071
- Medtronic-CapSure EPI
- Biotronik-ELC 54-UP

The following LV leads were bench tested for compatibility with BIOTRONIK's CRT-Ds:

- Guidant EasyTrak 4512 (unipolar)
- Guidant EasyTrak 4513 (bipolar)
- Guidant EasyTrak 3 4525 (bipolar)
- Medtronic Attain OTW 4193 (unipolar)
- Medtronic Attain OTW 4194 (bipolar)
- Medtronic Attain LV 2187 (unipolar)
- St. Jude Medical QuickSite 1056K (unipolar)
- ELA Situs OTW (unipolar)
- Biotronik Corox OTW 75-UP Steroid #346542 (unipolar)
- Biotronik Corox+ LV-H 75-BP #341885 (bipolar)

High Output Settings – High ventricular or biventricular pacing voltage settings may reduce the life expectancy of the CRT-D to less than 1 year. Programming of pulse amplitudes, higher than 4.8V, in combination with long pulse widths and/or high pacing rates may lead to early activation of replacement indicators.

Programming Wand Positioning – It is possible that significant movement of the programmer wand during VT/VF induction testing (with a manual shock) may result in a loss of communication between the CRT-D and the programmer. This situation can result in VT/VF therapy being deactivated. If this situation occurs, delivery of another manual shock or leaving and returning to the EP Test screen on the programmer will reactivate VT/VF detection and therapy.

Resuscitation Availability - Do not perform induction testing unless an alternate source of patient defibrillation such as an external defibrillator is readily available. In order to implant the CRT-D system, it is necessary to induce and convert the patient's ventricular tachyarrhythmias.

Unwanted Shocks – Always program the therapy status to DISABLED prior to handling the device to prevent the delivery of serious shocks to the patient or the person handling the device during the implant procedure.

Rate-Adaptive Pacing – Use rate-adaptive pacing with care in patients unable to tolerate increased pacing rates.

1.4.1 Sterilization, Storage, and Handling

Device Packaging - Do not use the device if the device's packaging is wet, punctured, opened or damaged because the integrity of the sterile packaging may be compromised. Return the device to BIOTRONIK.

Re-sterilization - Do not re-sterilize and re-implant explanted devices.

Storage (temperature) - Store the device between 5° to 55°C (41° - 131° F) because temperatures outside this range could damage the device.

Storage (magnets) - To avoid damage to the device, store the device in a clean area, away from magnets, kits containing magnets, and sources of electromagnetic interference (EMI).

Temperature Stabilization - Allow the device to reach room temperature before programming or implanting the device because temperature extremes may affect initial device function.

Use Before Date - Do not implant the device after the USE BEFORE DATE because the device may have reduced longevity.

1.4.2 Device Implantation and Programming

Blind Plug - A blind plug must be inserted and firmly connected into any unused header port to prevent chronic fluid influx and possible shunting of high energy therapy.

Capacitor Reformation - Infrequent charging of the high voltage capacitors may extend the charge times of the CRT-D. Therefore, the device automatically performs a capacitor reform at least every 3 months. The capacitors may also be reformed manually. For further information, please refer to Section 2.7.3 Capacitor Reforming.

Connector Compatibility - CRT-D and lead system compatibility should be confirmed prior to the implant procedure. Consult your BIOTRONIK representative regarding lead/pulse generator compatibility prior to the implantation of a CRT-D system. For further information, please refer to Appendix A.

ERI (Elective Replacement Indicator) - Upon reaching ERI, the battery has sufficient energy remaining to continue monitoring for at least three months and to deliver a minimum of six 30 joule shocks. After this period, all tachyarrhythmia detection and therapy is disabled. Bradycardia functions are still active at programmed values until the voltage of the 6.3 volt battery drops below 3.0 volts.

Magnets - Positioning of a magnet or the programming wand over the CRT-D will suspend tachycardia detection and treatment. The minimum magnet strength required to suspend tachycardia treatment is 1.8 mT. When the magnet strength decreases to less than 1 mT, the reed contact is reopened.

Pacemaker/CRT-D Interaction - In situations where a CRT-D and a pacemaker are implanted in the same patient, interaction testing should be completed. If the interaction between the CRT-D and the pacemaker cannot be resolved through repositioning of the leads or reprogramming of either the pacemaker or the CRT-D, the pacemaker should not be implanted (or explanted if previously implanted).

Programmed Parameters – Program the device parameters to appropriate values based on the patient's specific arrhythmias and condition.

Programmers - Use only BIOTRONIK programmers to communicate with the device (TMS 1000 ^{PLUS}, or EPR 1000 ^{PLUS}).

Sealing System - Failure to properly insert the torque wrench into the perforation at an angle perpendicular to the connector receptacle may result in damage to the sealing system and its self-sealing properties.

Defibrillation Threshold - Be aware that the changes in the patient's condition, drug regimen, and other factors may change the defibrillation threshold (DFT) which may result in non-conversion of the arrhythmia post-operatively. Successful conversion of ventricular fibrillation or ventricular tachycardia during arrhythmia conversion testing is no assurance that conversion will occur post-operatively.

Manual Shocks – User-commanded shocks may be withheld if the CRT-D is already busy processing a manual command or the Battery Status is low.

Charge Time - When preparing a high energy shock the charge circuit stops charging the capacitors after 20 seconds, and delivers the stored energy as shock therapy. After the device reaches ERI the stored energy may be less than 30 joules per shock.

Shock Impedance - If the shock impedance is less than twenty-five ohms, reposition the lead system to allow a greater distance between the electrodes. Never implant the device with a lead system that has measured shock impedance as less than twenty-five ohms. Damage to the device may result.

1.4.3 Lead Evaluation and Connection

Capping Leads - If a lead is abandoned rather than removed, it must be capped to ensure that it is not a pathway for currents to or from the heart.

Gripping Leads - Do not grip the lead with surgical instruments or use excessive force or surgical instruments to insert a stylet into a lead.

Kinking Leads - Do not kink leads. This may cause additional stress on the leads that can result in damage to the lead.

Liquid Immersion - Do not immerse leads in mineral oil, silicone oil, or any other liquid.

Short Circuit - Ensure that none of the lead electrodes are in contact (a short circuit) during delivery of shock therapy as this may cause current to bypass the heart or cause damage to the CRT-D system.

Straight Atrial Leads - When using a straight atrial lead e.g. non-preformed "J", a 1-month waiting period is recommended prior to programming atrial HF Burst therapy. This important consideration is related to the increased likelihood of atrial lead dislodgement during the first month after implant. A dislodged straight atrial lead could potentially fall in the ventricle and could subsequently result in the delivery of an undesired ventricular HF burst.

Far-field sensing of signals from the atrium in the ventricular channel or ventricular signals in the atrial channel should be avoided by appropriate lead placement, programming of pacing/sensing parameters, and maximum sensitivity settings. If it is necessary to lengthen A BLANK-V PACE or A BLANK-V SENSE, the parameter should be lengthened only long enough to eliminate far-field sensing as evidenced on the IEGMs. Extending either parameter unnecessarily may cause undersensing of actual atrial or ventricular events.

Suturing Leads - Do not suture directly over the lead body as this may cause structural damage. Use the appropriate suture sleeve to immobilize the lead and protect it against damage from ligatures.

Tricuspid Valve Bioprothesis - Use ventricular transvenous leads with caution in patients with a tricuspid valvular bioprosthesis.

Setscrew Adjustment – Back-off the setscrew(s) prior to insertion of lead connector(s) as failure to do so may result in damage to the lead(s), and/or difficulty connecting lead(s).

Cross Threading Setscrew(s) – To prevent cross threading the setscrew(s), do not back the setscrew(s) completely out of the threaded hole. Leave the torque wrench in the slot of the setscrew(s) while the lead is inserted.

Tightening Setscrew(s) – Do not overtighten the setscrew(s). Use only the BIOTRONIK supplied torque wrench.

Sealing System – Be sure to properly insert the torque wrench into the perforation at an angle perpendicular to the connector receptacle. Failure to do so may result in damage to the plug and its self-sealing properties.

1.4.4 Follow-up Testing

Defibrillation Threshold - Be aware that changes in the patient's condition, drug regimen, and other factors may change the defibrillation threshold (DFT), which may result in non-conversion of the arrhythmia post-operatively. Successful conversion of ventricular fibrillation or ventricular tachycardia during arrhythmia conversion testing is no assurance that conversion will occur post-operatively.

Resuscitation Availability - Ensure that an external defibrillator, and medical personnel, skilled in cardiopulmonary resuscitation (CPR), are present during post-implant device testing, should the patient require external rescue.

Safe Program – Within the EP Test screen, pressing the "Safe Program" key on the programmer head does not immediately send the safe program to the CRT-D. Pressing the "Safe Program" key activates the emergency function screen, but an additional screen touch is required to send the safe program to the CRT-D.

1.4.5 Pulse Generator Explant and Disposal

Device Incineration - Never incinerate the CRT-D due to the potential for explosion. The CRT-D must be explanted prior to cremation.

Explanted Devices - Return all explanted devices to BIOTRONIK.

Unwanted Shocks – Always program the therapy status to DISABLED prior to handling the device to prevent the delivery of serious shocks to the patient or the person handling the device during the implant procedure.

1.4.6 Hospital and Medical Hazards

Electromagnetic interference (EMI) signals present in hospital and medical environments may affect the function of any CRT-D, ICD or pacemaker. The CRT-D is designed to selectively filter out EMI noise. However, due to the variety of EMI signals, absolute protection from EMI is not possible with this or any other CRT-D or ICD.

The CRT-D system should be checked after any of the following medical procedures:

Diathermy - Diathermy therapy is not recommended for CRT-D or ICD patients due to possible heating effects of the pulse generator and at the implant site. If diathermy therapy must be used, it should not be applied in the immediate vicinity of the pulse generator or lead system.

Electrocautery - Electrosurgical cautery could induce ventricular arrhythmias and/or fibrillation, or may cause device malfunction or damage. If use of electrocautery is necessary, the current path and ground plate should be kept as far away from the pulse generator and leads as possible (at least 6 inches (15 cm)).

External Defibrillation - The device is protected against energy normally encountered from external defibrillation. However, any implanted device may be damaged by external defibrillation procedures. In addition, external defibrillation may also result in permanent myocardial damage at the electrode-tissue interface as well as temporary or permanent elevated pacing thresholds. When possible, observe the following precautions:

- Position the adhesive electrodes or defibrillation paddles of the external defibrillator anterior-posterior or along a line perpendicular to the axis formed by the implanted device and the heart.
- Set the energy to a level not higher than is required to achieve defibrillation.
- Place the paddles as far as possible away from the implanted device and lead system.
- After delivery of an external defibrillation shock, interrogate the CRT-D to confirm device status and proper function.

Lithotripsy - Lithotripsy may damage the CRT-D. If lithotripsy must be used, avoid focusing near the CRT-D implant site.

MRI (Magnetic Resonance Imaging) - Do not expose a patient to MRI device scanning. Strong magnetic fields may damage the device and cause injury to the patient.

Radiation - High radiation sources such as cobalt 60 or gamma radiation should not be directed at the pulse generator. If a patient requires radiation therapy in the vicinity of the pulse generator, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.

RF Ablation - Prior to performing an ablation procedure, deactivate the CRT-D during the procedure. Avoid applying ablation energy near the implanted lead system whenever possible.

1.4.7 Home and Occupational Hazards

Patients should be directed to avoid devices that generate strong electromagnetic interference (EMI) or magnetic fields. EMI could cause device malfunction or damage resulting in non-detection or delivery of unneeded therapy. Moving away from the source or turning it off will usually allow the CRT-D to return to its normal mode of operation.

The following equipment (and similar devices) may affect normal CRT-D operation: electric arc or resistance welders, electric melting furnaces, radio/television and radar transmitters, power-generating facilities, high-voltage transmission lines, and electrical ignition systems (of gasoline-powered devices) if protective hoods, shrouds, etc., are removed.

1.4.8 Cellular Phones

Testing has indicated there may be a potential interaction between analog cellular phones and BIOTRONIK CRT-D systems. Potential effects may be due to either the analog cellular phone signal or the magnet within the telephone and may include inhibition of therapy when the telephone is within 6.0 inches (15 cm) of the CRT-D, when the CRT-D is programmed to standard sensitivity.

Patients having an implanted BIOTRONIK CRT-D who operate an analog cellular telephone should:

- Maintain a minimum separation of 6.0 inches (15 cm) between a hand-held personal cellular telephone and the implanted device.
- Set the telephone to the lowest available power setting, if possible.
- Patients should hold the phone to the ear opposite the side of the implanted device. Patients should not carry the telephone in a breast pocket or on a belt over or within 6.0 inches (15 cm) of the implanted device as some telephones emit signals when they are turned ON, but not in use (i.e., in the listen or stand-by mode). Store the telephone in a location opposite the side of implant.

Based on results to date, adverse effects resulting from interactions between cellular telephones and implanted CRT-D s have been transitory. The potential adverse effects could include inhibition or delivery of additional therapies. If electromagnetic interference (EMI) emitting from a telephone does adversely affect an implanted CRT-D, moving the telephone away from the immediate vicinity of the CRT-D should restore normal operation. A recommendation to address every specific interaction of EMI with implanted CRT-D s is not possible due to the disparate nature of EMI.

1.4.9 Electronic Article Surveillance (EAS)

Equipment such as retail theft prevention systems may interact with pulse generators. Patients should be advised to walk directly through and not to remain near an EAS system longer than necessary.

1.4.10 Home Appliances

Home appliances normally do not affect CRT-D operation if the appliances are in proper working condition and correctly grounded and shielded. There have been reports of the interaction of electric tools or other external devices (e.g. electric drills, older models of microwave ovens, electric razors, etc.) with CRT-D s when they are placed in close proximity to the device.

1.5 Potential and Observed Effects of the Device on Health

1.5.1 Potential Adverse Events

The following are possible adverse events that may occur relative to the implant procedure and chronic implant of the CRT-D:

- Air embolism
- Allergic reactions to contrast media
- Arrhythmias
- Bleeding
- Body rejection phenomena
- Cardiac tamponade
- Chronic nerve damage
- Damage to heart valves
- Device migration
- Elevated pacing thresholds
- Extrusion
- Fluid accumulation
- Hematoma
- Infection
- Keloid formation
- Lead dislodgment
- Lead fracture/ insulation damage
- Lead-related thrombosis
- Local tissue reaction/fibrotic tissue formation
- Muscle or nerve stimulation
- Myocardial damage
- Myopotential sensing
- Pacemaker mediated tachycardia
- Pneumothorax
- Pocket erosion
- Thromboembolism
- Undersensing of intrinsic signals
- Venous occlusion
- Venous or cardiac perforation

In addition, patients implanted with the CRT-D system may have the following risks. These are the same risks that are present with implantation of any CRT-D system:

- Acceleration of arrhythmias (speeding up heart rhythm caused by the CRT-D)
- Dependency
- Depression
- Fear of premature battery depletion (fear that battery will stop working before predicted time)
- Fear of shocking while awake
- Fear that shocking ability may be lost
- Anxiety about the CRT-D resulting from frequent shocks
- Imagined shock (phantom shock)
- Inappropriate detection of ventricular arrhythmias
- Inappropriate shocks
- Potential death due to inability to defibrillate or pace
- Shunting current or insulating myocardium during defibrillation with external or internal paddles

There may be other risks associated with this device that are currently unforeseeable.

1.5.2 Observed Adverse Events

The OPTION CRT/ATx study was a prospective, randomized, multi-center study to demonstrate the safety and effectiveness of the investigational Tupos LV/ATx Cardiac Resynchronization Therapy Defibrillator (CRT-D) in patients with congestive heart failure (CHF) and atrial tachyarrhythmias. All patients enrolled into the clinical study were randomly assigned to either the study group or the control group at a 2 to 1 ratio. Patients in the study group were implanted with the Tupos LV/ATx. Patients in the control group were implanted with a legally marketed ICD that provides CRT.

Of the 278 adverse events reported in the Tupos LV/ATx study group, there have been 210 observations in 104 patients and 68 complications in 50 patients with a cumulative implant duration of 1240.4 months (101.9 patient-years). 37.6% of the enrolled study patients have experienced a complication. The rate of complications per patient-year is 0.67. 78.2% of the enrolled study patients have a reported observation. The rate of observations per patient-year is 2.06.

Complications and observations for the Tupos LV/ATx study group are summarized in Table 1 and Table 2. The total number of patients may not equal the sum of the number of patients listed in each category, as an individual patient may have experienced more than one complication or observation.

Table 1: Summary of Complications – Tupos LV/ATx

Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Procedure Related				
Hematoma	4	3.01%	4	0.04
Pneumothorax	2	1.50%	2	0.02
Total	**6**	**4.51%**	**6**	**0.06**
Atrial Lead Related				
Dislodgement	3	2.26%	3	0.03
Total	**3**	**2.26%**	**3**	**0.03**
ICD Lead Related				
High threshold/ No capture	2	1.50%	2	0.02
Diaphragmatic/ Intercostal stimulation (RV)	1	0.75%	1	0.01
Total	**3**	**2.26%**	**3**	**0.03**

Table 1: Summary of Complications – Tupos LV/ATx				
Category	**Number of Patients**	**% of Patients**	**Number of Complications**	**Complications per patient-year**
LV Lead Related				
High threshold/ Intermittent biventricular capture/ No capture	11	8.27%	12	0.12
Unable to implant lead via coronary sinus	11	8.27%	11	0.11
Dislodgement	4	3.01%	4	0.04
Diaphragmatic/ Intercostal stimulation	1	0.75%	2	0.02
Total	**27**	**20.30%**	**29**	**0.28**
Device Related				
Infection	3	2.26%	7	0.07
Device migration	4	3.01%	4	0.04
Elective replacement indicator reached	4	3.01%	4	0.04
Inductions and conversions	1	0.75%	1	0.01
Unable to interrogate device	1	0.75%	1	0.01
Total	**12**	**9.02%**	**17**	**0.17**
Total Procedure and Device Related	**43**	**32.33%**	**58**	**0.57**

Table 1: Summary of Complications – Tupos LV/ATx				
Category	Number of Patients	% of Patients	Number of Complications	Complications per patient-year
Other Medical Related				
Non-CHF Cardiac Symptoms	4	3.01%	4	0.04
Ventricular arrhythmias	2	1.50%	3	0.03
Other medical	2	1.50%	2	0.02
Atrial arrhythmia	1	0.75%	1	0.01
Total	**9**	**6.77%**	**10**	**0.10**
Total – All Patients and Categories	**50**	**37.59%**	**68**	**0.67**

Number of Patients = 133, Number of Patient-Years = 101.9

* 1 Unanticipated Adverse Device Effect (UADE) occurred with a Tupos LV/ATx CRT-D during the OPTION clinical study. The device was explanted after it was unable to be interrogated with the programmer software and no pacing output was evident. The analysis showed an appropriately depleted battery and no anomalies with the IC module. The battery depletion strongly suggests that the high voltage circuit was activated over a prolonged period due to a single-bit execution path failure. The current programmer software with Automatic Battery Management (ABM) would have prevented the battery from becoming completely depleted. There were no other instances of this failure mechanism in Tupos LV/ATx devices.

For the Tupos LV/ATx study group, there were 210 observations in 104 patients with cumulative implant duration of 1240.4 months (101.9 patient years). 78.2% of the enrolled study patients have a reported observation. The rate of observations per patient-year was 2.06. Table 2 summarizes by category each type of observation for the study group.

Table 2: Summary of Observations—Tupos LV/ATx				
Category	**Number of Patients**	**% of Patients**	**Number**	**per patient-year**
Procedure Related				
Hematoma	10	7.52%	10	0.10
Cardiac arrest	2	1.50%	2	0.02
Unable to implant system	1	0.75%	1	0.01
Total	**13**	**9.77%**	**13**	**0.13**
Atrial Lead Related				
Dislodgement	1	0.75%	1	0.01
High threshold	1	0.75%	1	0.01
Total	**2**	**1.50%**	**2**	**0.02**
ICD Lead Related				
High threshold/No capture	1	0.75%	1	0.01
Total	**1**	**0.75%**	**1**	**0.01**
LV Lead Related				
High threshold/ Intermittent biventricular capture/ No capture	24	18.05%	24	0.24
Diaphragmatic/ Intercostal stimulation	8	6.02%	8	0.08
Total	**30**	**22.56%**	**32**	**0.31**

Table 2: Summary of Observations – Tupos LV/ATx				
Category	**Number of Patients**	**% of Patients**	**Number**	**per patient-year**
Device Related				
Infection	1	0.75%	1	0.01
Inductions and conversions	6	4.51%	6	0.06
Inappropriate sensing	20	15.04%	20	0.20
Symptomatic with biventricular pacing	2	1.50%	2	0.02
Total	**25**	**18.80%**	**29**	**0.28**
Total Procedure, Lead and Device Related	**61**	**45.86%**	**77**	**0.76**
Other Medical Related				
Non-CHF Cardiac Symptoms	21	15.79%	21	0.21
Ventricular arrhythmias	11	8.27%	11	0.11
Other medical	26	19.55%	32	0.31
Atrial arrhythmia	14	10.53%	14	0.14
Dizziness	4	3.01%	4	0.04
Medication	5	3.76%	5	0.05
Worsening CHF	46	34.59%	46	0.45
Total	**82**	**61.65%**	**133**	**1.31**
Total – All Patients and Categories	**104**	**78.20%**	**210**	**2.06**

Number of Patients = 133 Number of Patient-Years = 101.9

There have been 4 patient deaths reported for the control group (out of 67 total control patients) and 10 patient deaths have been reported for the study group (out of 133 total study patients). None of the deaths were related to the implanted CRT-D system. One patient in the control group died prior to receiving a biventricular device implant. There is no significant difference between the number of deaths in the study group versus the control group (p = 0.777, Fisher's Exact Test, 2 sided). Table 3 provides a summary of reported patient deaths and Table 4 provides survival percentages by follow-up interval during the first 12 months of study participation.

Table 3: Summary of Patient Deaths

Category of Death	Study (N = 133)	Control (N = 67)
	Number of Patients	Number of Patients
Sudden Cardiac	1	1
Non-Sudden Cardiac	5	2
Non-Cardiac	4	1
All Causes	10	4

Figure 1 shows the associated Kaplan-Meier survival curves for the study and control group. The significance level for the difference between the two study groups based on a Log Rank test was p = 0.795.

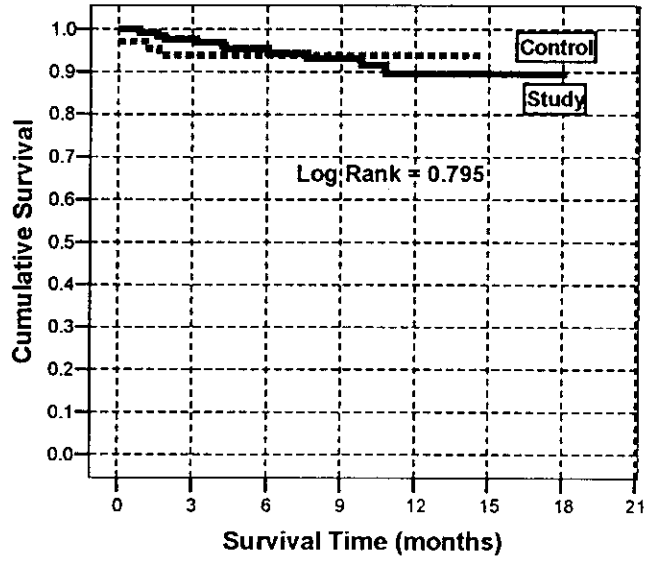


Figure 1: Kaplan-Meier Survival Curves

Table 4 Survival Table

	Study Group (n = 133)		Control Group (n = 66)	
	Number	%	Number	%
Enrollment	133	100.00%	67	100.00%
3-month	131	98.50%	63	94.03%
6-month	127	95.49%	63	94.03%
12-month	123	92.48%	63	94.03%

1.6 Tupos LV/ATx Clinical Study

1.6.1 Study Overview

The purpose of the prospective, randomized, multi-center OPTION CRT/ATx study was to demonstrate the safety and effectiveness of the investigational Tupos LV/ATx Cardiac

Resynchronization Therapy Defibrillator (CRT-D) in patients with congestive heart failure (CHF) and atrial tachyarrhythmias. Patients in the study group were implanted with a BIOTRONIK Tupos LV/ATx. Patients in the control group were implanted with any legally marketed CRT-D. Patients in both the study and control groups were implanted with a legally marketed left ventricular lead.

1.6.2 Methods

Primarily, the study evaluates and compares the functional benefits of CRT between the two randomized groups using a composite endpoint consisting of a six-minute walk test (meters walked) and quality of life measurement (assessed using the Minnesota Living with Heart Failure Questionnaire). Relevant measurements were completed twice for each patient: once at the Baseline evaluation (two-week post implant follow-up) and again at a six-month follow-up evaluation. The data collected during this clinical study was used to demonstrate equivalent treatment of CHF in both the study and control groups. This study also evaluated other outcomes including: the effectiveness of atrial therapy to automatically convert atrial tachyarrhythmias, the percentage of time CRT is delivered, and other measures of CHF status including NYHA classification, peak oxygen consumption during metabolic exercise testing, and the rate of hospitalization for CHF.

1.6.3 Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Stable, symptomatic CHF status
- NYHA Class III or IV congestive heart failure
- Left ventricular ejection fraction ≤ 35% (measured within Six-Months prior to enrollment)
- Intraventricular conduction delay (QRS duration greater than or equal to 130 ms)

- For patients with an existing ICD, optimal and stable CHF drug regimen including ACE-inhibitors and beta-blockers unless contraindicated (stable is defined as changes in dosages less than 50% during the last 30 days)
- Indicated for ICD therapy
- History or significant risk of atrial tachyarrhythmias
- Willing to receive possibly uncomfortable atrial shock therapy for the treatment of atrial tachyarrhythmias
- Able to understand the nature of the study and give informed consent
- Ability to tolerate the surgical procedure required for implantation
- Ability to complete all required testing including the six-minute walk test and cardiopulmonary exercise testing
- Available for follow-up visits on a regular basis at the investigational site
- Age greater than or equal to 18 years

1.6.4 Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following:

- Previously implanted CRT device
- ACC/AHA/NASPE indication for bradycardia pacing (sinus node dysfunction)
- Six-minute walk test distance greater than 450 meters
- Chronic atrial tachyarrhythmias refractory to cardioversion shock therapy
- Receiving intermittent, unstable intravenous inotropic drug therapy (patients on stable doses of positive inotropic outpatient therapy for at least One-Month are permitted)
- Enrolled in another cardiovascular or pharmacological clinical investigation
- Expected to receive a heart transplant within 6 months
- Life expectancy less than 6 months

- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Acute myocardial infarction, unstable angina or cardiac revascularization within the last 30 days prior to enrollment
- Conditions that prohibit placement of any of the lead systems

1.6.5 Summary of Clinical Results

A total of 200 patients were enrolled in the OPTION CRT/ATx clinical study at 25 sites:

There were 133 study patients and 67 active control patients in this prospective, multi-center, randomized clinical study. For the study group, there were 129 successful implants (91.4%) of the Tupos LV/ATx CRT-D system. For the active control group, there were 64 successful implants (92.2%) of the legally marketed CRT-D systems.

1.6.6 Patient Accountability

After randomization and enrollment, 7 patients (4 in the study group and 3 in the control group) did not receive an implant. The reasons for patients not receiving an implant are outlined in Figure 2.

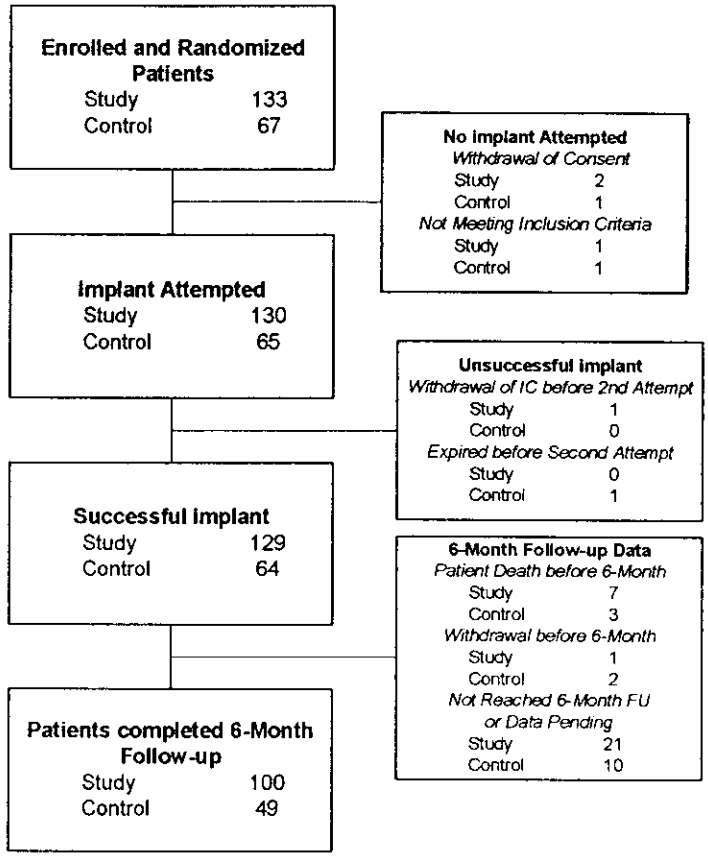


Figure 2: Patient Accountability

1.6.7 Overall Results

- There were 192 endocardial and 19 epicardial leads implanted in 193 patients. Investigators were allowed to choose among any legally marketed LV lead according to familiarity with the lead and patient anatomy. The Tupos LV/ATx CRT-D was implanted with 7 endocardial and 4 epicardial lead models from 6 different manufacturers. There were no adverse events reported attributable to lead-generator incompatibility.

- The cumulative implant duration was 1240.4 months with a mean duration of 9.6 months for the study group. The cumulative implant duration is 596.5 months with a mean duration of 9.3 months for the control group.
- For the study group, there have been 278 adverse events (210 observations in 104 patients and 68 complications in 50 patients). There has been one unanticipated adverse device effect reported.
- For the control group, there have been 105 adverse events (81 observations in 44 patients and 24 complications in 19 patients). There have been no unanticipated adverse device effects reported.
- There have been 10 patient deaths reported in the study group and 4 patient deaths reported in the control group. The clinical investigators have determined that no deaths were related to the study device.

1.6.7.1 Primary Endpoint 1: Six Minute Walk Test & QOL (Effectiveness)

The purpose of Primary Endpoint 1 is to evaluate the effectiveness of the Tupos LV/ATx system in providing CRT as measured by the average composite rate of improvement in six minute walk test and QOL.

Table 5 presents the average composite rate of improvement in six minute walk test distance and QOL score, the average 6-minute walk test distance and the average QOL score at Baseline and at the Six-Month follow-up, as well as the average difference in 6-minute walk test distance and QOL score between Baseline and the Six-Month follow-up for the Study and Control Groups for those patients with six minute walk test data and complete QOL data at both Baseline and the Six-Month follow-up.

Table 5: Composite of Six Minute Walk Test and QOL (Effectiveness)

Category	Study Group (N = 74) Mean ± SE	Control Group (N = 38) Mean ± SE	P-value*
Distance Walked at Baseline	310.51 ± 10.89	288.76 ± 15.37	0.249
Distance Walked at Six-Months	340.77 ± 12.32	301.84 ± 17.02	0.067
Δ Distance Walked	30.26 ± 10.40 17.27% ± 5.59%	13.08 ± 13.05 8.71% ± 5.26%	0.322 0.326
QOL Score at Baseline	44.39 ± 2.78	45.53 ± 4.13	0.817
QOL Score at Six-Months	28.68 ± 2.66	33.95 ± 4.35	0.279
Δ in QOL Score**	15.72± 2.83 19.08% ± 12.21%	11.58 ± 3.45 -13.42% ± 34.54%	0.376 0.281
Composite Rate*	**18.18% ± 7.07%**	**-2.36% ± 17.73%**	**0.030**

*The calculated p-values are associated with a Student's t-test (2-sided) of the equality of means in the two groups, except for the p-value of the composite rate, which is associated with a test of equivalence (non-inferiority).

**Δ in QOL Score is calculated as the average of the individual differences between Baseline and Six-Months for each patient. Negative values for mean Δ QOL in percent are possible when positive mean values for absolute changes in QOL are recorded. In some cases, small, negative changes in absolute QOL scores resulted in relatively large percentage changes.

***The Composite Rate (=(Δ Distance Walked (%) + Δ QOL Score (%)) / 2) is calculated for each patient and then averaged to obtain the Composite Rates. For all calculations, a positive number represents improvement from Baseline to Six-Months.

1.6.8 Effectiveness Endpoint Analysis and Conclusions

A composite rate of six minute walk test and QOL improvement from Baseline to the Six-Month follow-up is evaluated as a measure of CRT effectiveness. For this analysis both six minute walk test and QOL are equally weighted at 50%.

The mean difference in the composite rate between study and control group was 20.53% with an associated one-sided, 95% confidence bound is (-6.10%). The p-value for non-inferiority within 10% is 0.030. The analysis of the composite rate in six minute walk test distance and QOL score demonstrates that the study group is non-inferior to the control group and that the primary effectiveness endpoint was met (p=0.030).

1.6.9 Primary Endpoint (Safety):Complication-Free Rate

The purpose of Primary Endpoint 2 was to evaluate complications (adverse events that require additional invasive intervention to resolve) related to the implanted CRT system which includes the Tupos LV/ATx, the right atrial lead, the right ventricular ICD lead, the left ventricular lead, and the implant procedure. The target complication-free rate at Six-Months is 85%.

Table 6 provides the categorized complication rates at 6-months for the study and the control group as well as a comparison between the study and the control group.

Table 6: Complications at 6-Month – Study and Control					
Category	Study N = 133	Control N = 67	Study versus Control Comparison		
			Delta	95% CI	P-value
Procedure Related	6 (4.51%)	1 (1.49%)	3.02%	[-3.64%, 8.45%]	0.428
Atrial Lead Related	3 (2.26%)	1 (1.49%)	0.76%	[-5.74%, 5.37%]	1.000
ICD Lead Related	3 (2.26%)	0 (0%)	2.26%	[-3.03%, 6.53%]	0.552
LV Lead Related	26 (19.55%)	9 (13.43%)	6.12%	[-5.50%, 16.45%]	0.329
Device Related	7 (5.26%)	5 (7.46%)	-2.20%	[-11.42%, 4.77%]	0.541
Other Medical Related	9 (6.77%)	2 (2.99%)	3.78%	[-3.82%, 10.13%]	0.341
Total Procedure, Lead and Device Related	39 (29.32%)	15 (22.39%)	6.94%	[-6.46%, 19.17%]	0.317
Total	**46 (34.59%)**	**17 (25.37%)**	**9.21%**	**[-4.96%, 21.99%]**	**0.201**

1.6.10 Primary Safety Enpoint Analysis and Conclusions

The observed procedure, lead and device related complication-free rate at 6 months was 70.68%. The 95% confidence interval for the complication-free rate was [62.16%, 78.25%]. The lower, one-sided 95% confidence bound for the complication-free rate was 63.50%. Therefore the procedure, lead and device related complication-free rate at 6 months did not meet the pre-specified acceptance criterion for this endpoint.

1.6.11 Post-hoc Safety Analysis

BIOTRONIK did not meet the pre-specified objective performance criteria of 85% within 10% for the safety endpoint. Therefore, a post-hoc safety analysis was conducted. It was noted that 79.80% (39 out of 49 events) of the complications were right atrial lead, right ventricular ICD lead, left ventricular lead and procedure related. The atrial, ICD and LV leads used during this study are legally marketed devices.

This post-hoc analysis evaluated the LV lead complications that were "related" or "possibly related" to the Tupos LV/ATx CRT-D, but excludes the complications that were "not related" to the Tupos LV/ATx device (see **Table 7**). There were 11 patients who had an attempt to implant the LV lead, but the physician was unsuccessful in either obtaining coronary sinus (CS) access or unable to find a stable position for the LV lead. Additionally, there were 4 patients with a documented LV lead dislodgement that has no direct relationship to the implanted Tupos LV/ATx.

Table 7: Complications at 6-Months (Excluding LV Lead Related) - Study versus Control

Category	Study N=133	Control N=67	Difference Study vs Control
Procedure Related	6 (4.51%)	2 (2.99%)	1.53%
Atrial Lead Related	3 (2.26%)	1 (1.49%)	0.76%
ICD Lead Related	3 (2.26%)	0 (0%)	2.26%
LV Lead Related	11 (8.27%)	1 (1.49%)	6.78%
Device Related	7 (5.26%)	5 (7.46%)	-2.20%
Other Medical Related	9 (6.77%)	2 (2.99%)	3.78%
Total Procedure, Lead and Device Related	27 (20.30%)	8 (11.94%)	8.36%
Total	**35 (26.32%)**	**10 (14.93%)**	**11.39%**

The pulse generator related complication rate is higher in the control group as compared to the study group. The complication rates for procedure related, atrial lead related, ICD lead related, LV lead related and other medical related are higher in the study group as compared to the control group.

1.6.12 Post hoc Safety Analysis Conclusion

There are no clinically substantial differences in the total complication rate or in the rates for the different complication rate categories between the study and the control group.

Table 8 compares this post-hoc Safety Endpoint analysis to previous CRT-D clinical studies:

Table 8 Safety Endpoint Comparisons

CRT-D Study	Estimated freedom from Complications @ 6mos.	Lower 95% CI	95% lower bound criteria
BIOTRONIK OPTION (Original Analysis)	70.68%	63.5%	75%
BIOTRONIK OPTION (Post-hoc Analysis)	78.95%	72.29%	75%
Medtronic Insync ICD	81.1%	77.6%	67%
Guidant Contak CD	N/A	N/A	70%
St. Jude Medical Epic HF	93.4%	90.6%	70%

This analysis confirms that the safety profile of the Tupos LV/ATx is within a similar range determined during trials of other legally marketed CRT D devices.

1.6.13 Secondary Endpoint Results

1. The purpose of Secondary Endpoint 1 is to evaluate the overall ability of the Tupos LV/ATx to appropriately convert spontaneous AT (atrial tachycardia) and AF (atrial fibrillation). The results from the OPTION study were compared to the results from BIOTRONIK's TACT study (P000009/S4, dated

09-09-2002) that demonstrated the effectiveness of these atrial therapy features in the Tachos DR - Atrial Tx ICD.

Table 9 summarizes success rates for each individual atrial tachyarrhythmia therapy type and overall success rate from the OPTION study compared to the TACT study. The number of episodes and patients receiving any therapy is less than the total episodes of each therapy type, as episodes may have included more than one type of therapy.

Table 9 Overall Atrial Conversion Rate

Patients	OPTION Study			
	Patients	Success	Episodes	Conversion rate
ATP	3	3	5	60.0%
HF Burst	17	45	111	40.5%
Shock	12	30	34	88.2%
All Therapies	**25**	**78**	**129**	**60.5%**
TACT Study				
ATP	29	62	142	43.6 %
HF Burst	49	156	408	38.2 %
Shock	42	84	108	77.8 %
All Therapies	**66**	**302**	**542**	**55.7 %**

The overall conversion rate and the conversion rates for each therapy are comparable to the conversion rates observed in the TACT study, demonstrating that the Tupos LV/ATx device has similar atrial conversion capabilities as the legally marketed Tachos DR – Atrial Tx ICD.

2. The purpose of Secondary Endpoint 2 is to evaluate VT (ventricular tachycardia) and VF (ventricular fibrillation) detection times of the Tupos LV/ATx. This is a measure of the ability of the ventricular detection algorithm to detect VT and VF in an appropriate timeframe. This endpoint was evaluated based on the review of electrograms following induced VT/VF episodes. A comparison of data from the TACT study that utilized the legally marketed Tachos DR - Atrial Tx ICD (P000009/S4, dated 09-09-2002) to data

collected during the OPTION study for the Tupos LV/ATx was performed.

Table 10 summarizes and compares the results from these two clinical studies.

Table 10: Summary of Detection Times

Detection Time	Tachos DR - Atrial Tx ICD Mean (SE) / N	Tupos LV/ATx Mean (SE) / N	Difference
Individual Readings	2.27 (0.06) / 52	2.26 (0.06) / 71	0.01
By Patient	2.27 (0.07) / 26	2.24 (0.06) / 35	0.03

The analysis demonstrates that the average detection times of the Tupos LV/ATx are comparable to the detection times observed with the legally marketed Tachos DR - Atrial Tx ICD. Both devices utilize identical ventricular detection algorithms and only sense with the right ventricular lead. This clinical data demonstrates that the ventricular detection times are similar in both devices.

3. The purpose of Secondary Endpoint 3 is to evaluate the percentage of ventricular pacing (thus, CRT) as demonstrated by the device diagnostics at required follow-ups. This data was based on diagnostic data stored by the Tupos LV/ATx.

   Table 11 summarizes the percentage of ventricular pacing between follow-ups as shown by device diagnostics for patients in the study group.

Table 11: Percentage of Ventricular Pacing – 3-Month and 6-Month Follow-ups

Percentage of Ventricular Pacing	3-Months Patients (percentage)	6-Months Patients (percentage)
<80%	9 (7.4%)	4 (4.0%)
81 – 85 %	4 (3.3%)	2 (2.0%)
86 – 90 %	13 (10.7%)	9 (9.1%)
91 – 95 %	19 (15.7%)	20 (20.2%)
96 – 100 %	76 (62.8%)	64 (64.7%)
Totals	**121 (100%)**	**99 (100%)**

The majority of the follow-ups (84.9%) show a percentage of ventricular pacing of 91% or more at Six-Months.

4. The purpose of secondary endpoint 4 is to evaluate improvement in functional capacity as measured by the six minute walk test. The six minute walk test is a well-accepted measure of functional capacity and exercise tolerance. Also, this test more closely mimics the patient's day-to-day activities than maximal exercise testing.

   Table 12 summarizes the six minute walk test distance at Baseline and the Six-Month follow-up for patients in the study group and the control group.

Table 12: Six Minute Walk Distance

Distance (meters)	Study	Control
Baseline		
N	127	61
Mean ± SE	283.14 ± 9.27	269.43 ± 13.77
Range	23 to 511	29 to 507
Median	302.00	244.00
Six-Month		
N	93	44
Mean ± SE	329.73 ± 10.82	310.70 ± 15.49
Range	78 to 596	91 to 489
Median	335.00	313.00

* Student's t-test, 2-sided

There are no clinically relevant differences in the six minute walk test results between the study and the control group.

5. The purpose of Secondary Endpoint 5 is to evaluate the improvement in the patient's NYHA classification. Table 13 summarizes the average improvement in NYHA from Baseline to Six-Months for 140 patients that were able to complete both NYHA classification evaluations.

Table 13: Improvement in NYHA Classification at Six-Months from Baseline

NYHA Change During OPTION Study		
Change in NYHA Class	Study Patients (N=97) (percentage)	Control Patients (N=43) (percentage)
Improved 2 classes	10 (10.3%)	2 (4.7%)
Improved 1 class	47 (48.5%)	20 (46.5%)
Total improved	57 (58.8%)	23 (51.2%)
No change	39 (40.2%)	20 (46.5%)
Worsened 1 class	1 (1.0%)	1 (2.3%)

The study and the control group have similar NYHA classes and similar rates of improvement in NYHA class from Baseline to the Six-Month follow-up.

6. The purpose of Secondary Endpoint 6 is to evaluate the rate of hospitalization, for CHF and for all other causes. The occurrence rate and reasons for hospitalization of the study group were compared to the control group. To be consistent with other large-scale clinical trials, clinical sites were instructed to report hospitalizations for CHF using the following definitions: 1) hospitalization for heart failure management, 2) outpatient visit in which IV inotropes or vasoactive infusion are administered continuously for at least 4 hours, or 3) emergency room (ER) visit of at least 12 hours duration in which intravenous heart failure medications including diuretics are administered.

Table 14 summarizes hospitalization, ER visits and outpatient visits for enrolled patients.

Table 14: Hospitalization, ER Visits and Outpatient Visits

Medical Visits	Study (N=128)	Control (N=65)
Hospital Admissions	**CHF Related:**	**CHF Related:**
Patients	20 (15.6%)	5 (7.7%)
Hospitalizations	28	9
	All causes:	**All causes:**
Patients	68 (53.1%)	29 (44.6%)
Hospitalizations	76	46
Emergency Room Visits	**CHF Related:**	**CHF Related:**
Patients	1 (0.8%)	0 (0.0%)
Visits	1	0
	All causes:	**All causes:**
Patients	13 (10.1%)	2 (3.1%)
Visits	16	2
Outpatient Visits	**CHF Related:**	**CHF Related:**
Patients	1 (0.8%)	0 (0.0%)
Visits	1	0
	All causes:	**All causes:**
Patients	5 (3.9%)	2 (3.1%)
Visits	5	2

A large percentage of All Cause hospitalizations can be attributed to pacing lead revisions, device infections, or other device-related interventions (e.g., pocket revision or device replacements for ERI or device recall). The CHF hospitalization rate for both the study and control groups is clinically acceptable considering the enrollment CHF status of the patients.

7. The purpose of Secondary Endpoint 7 is to evaluate the observation rate. Observations are defined as clinical events that do not require additional invasive intervention to resolve. For the study group, there were 210 observations in 104 patients with cumulative implant duration of 1240.4 months (101.9 patient years). 78.2% of the enrolled study patients

have a reported observation. The rate of observations per patient-year is 2.06. For the control group, there were 81 observations in 44 patients with cumulative implant duration of 596.5 months (49.0 patient years). 65.7% of the enrolled control patients had a reported observation. The rate of observations per patient-year was 1.65.

8. The purpose of Secondary Endpoint 8 is to evaluate peak VO2 as a measure of effectiveness of the Tupos LV/ATx system in providing CRT. The core lab was blinded to study randomization assignments during evaluation of the results of the cardiopulmonary exercise (CPX) testing in order to minimize the potential for bias. According to the protocol, to be included in the analysis, patients were required to attain a respiratory exchange ratio (RER) of ≥ 1.

   Table 15 provides a summary of peak VO_2 results for 42 patients with CPX testing completed at Baseline and the Six-Month follow-up and with an RER of ≥ 1.

Table 15: Peak VO2 Testing Results – Patients with RER ≥ 1

Results	Study	Control
Peak VO_2 (ml/kg/min)	**N=32** **Baseline:** Mean: 13.46 ± 0.57 Range: 6.9 to 21.1 **Six-Month:** Mean: 13.39 ± 0.53 Range: 7.6 to 20.70 **Difference:** Mean: -0.06 ± 0.42 Range: -7.9 to 4.9	**N=10** **Baseline:** Mean: 12.58 ± 0.75 Range: 8.0 to 14.8 **Six-Month:** Mean: 12.89 ± 0.94 Range: 7.0 to 17.2 **Difference:** Mean: 0.31 ± 0.67 Range: -2.7 to 4.6

1.6.14 Multi-site Poolability and Gender Analysis

The OPTION CRT/ATx clinical report includes data from multiple centers with centralized coordination, data processing, and reporting at BIOTRONIK. All of the clinical centers followed the requirements of an identical clinical protocol, and all of the clinical centers used the same methods to collect and report the clinical data. In order to justify pooling of the data from multiple centers, several analyses were completed. All of the centers were divided into two groups based on implant volume. Comparisons were then made between the patient populations based on the results of each of the endpoints. Additionally, analyses were performed on the data collected in the OPTION CRT/ATx clinical investigation in order to compare results between males and females. The first type of analysis compared enrollment by patient gender in each of the study and control groups. The second type of analysis compared effectiveness outcomes in each gender.

The results of these analyses demonstrate poolability of the data between sites. There were no significant differences in the second primary endpoint or any of the secondary endpoints between high and low volume implant centers.

The gender distribution in this clinical investigation is consistent within the study groups and includes a representative proportion of female participants. There were no significant differences in any of the primary or secondary endpoints between the male and female population.

1.6.15 Conclusions

The IDE Clinical study (OPTION LV/ATx) demonstrated that the safety and effectiveness of the Tupos LV/ATx CRT-ICD device is equivalent to that of similar legally marketed CRT-D devices. Although the study missed its primary safety endpoint, additional post hoc analyses were conducted to reassure that the safety profile of the device is comparable to other legally marketed CRT-D devices.

1.7 Patient Selection and Treatment

1.7.1 Individualization of Treatment

- Determine whether the expected device benefits outweigh the possibility of early device replacement for patients whose ventricular tachyarrhythmias require frequent shocks.
- Direct any questions regarding individualization of patient therapy to your BIOTRONIK representative or BIOTRONIK technical services at 1-800-547-0394.

The prospective patient's size and activity level should be evaluated to determine whether a pectoral or abdominal implant is suitable. It is strongly recommended that candidates for a CRT-D have a complete cardiac evaluation including EP testing prior to device implant to gather electrophysiologic information, including the rates and classifications of all the patient's cardiac rhythms. When gathering this information, delineate all clinically significant ventricular and atrial arrhythmias, whether they occur spontaneously or during EP testing.

If the patient's condition permits, use exercise stress testing to do the following:

- Determine the maximum rate of the patient's normal rhythm.
- Identify any supraventricular tachyarrhythmias.
- Identify exercise-induced tachyarrhythmias.

The maximum exercise rate or the presence of supraventricular tachyarrhythmias may influence selection of programmable parameters. Holter monitoring or other extended ECG monitoring also may be helpful.

If the patient is being treated with antiarrhythmic or cardiac drugs, the patient should be on a maintenance drug dose rather than a loading dose at the time of pulse generator implantation. If changes to drug therapy are made, repeated arrhythmia inductions are recommended to verify pulse generator detection and conversion. The pulse generator also may need to be reprogrammed.

Changes in a patient's antiarrhythmic drug or any other medication that affect the patient's normal cardiac rate or conduction can affect the rate of tachyarrhythmias and/or efficacy of therapy.

If another cardiac surgical procedure is performed prior to implanting the pulse generator, it may be preferable to implant the lead system at that time. This may prevent the need for an additional thoracic operation.

1.7.2 Specific Patient Populations

Pregnancy - If there is a need to image the device, care should be taken to minimize radiation exposure to the fetus and the mother.

Nursing Mothers - Although appropriate biocompatibility testing has been conducted for this implant device, there has been no quantitative assessment of the presence of leachables in breast milk.

Handicapped and Disabled Patients - Special care is needed in using this device for patients using electrical wheel chair or other electrical (external or implanted devices).

1.8 Patient Counseling Information

- The pulse generator is subject to random component failure. Such failure could cause inappropriate shocks, induction of arrhythmias or inability to sense arrhythmias, and could lead to the patient's death.
- Persons administering CPR may experience the presence of voltage on the patient's body surface (tingling) when the patient's CRT-D system delivers a shock.

A patient manual is available for the patient, patient's relatives, and other interested people. Discuss the information in the manual with concerned individuals both before and after pulse generator implantation so they are fully familiar with operation of the device. (For additional copies of the patient manual, contact the BIOTRONIK at the address listed in this manual.)

1.9 Evaluating Prospective CRT-D Patients

The prospective CRT-D implant candidate should undergo a cardiac evaluation to classify any and all tachyarrhythmias. In addition, other patient specific cardiac information will help in selecting the optimal device settings. This evaluation may include, but is not limited to:

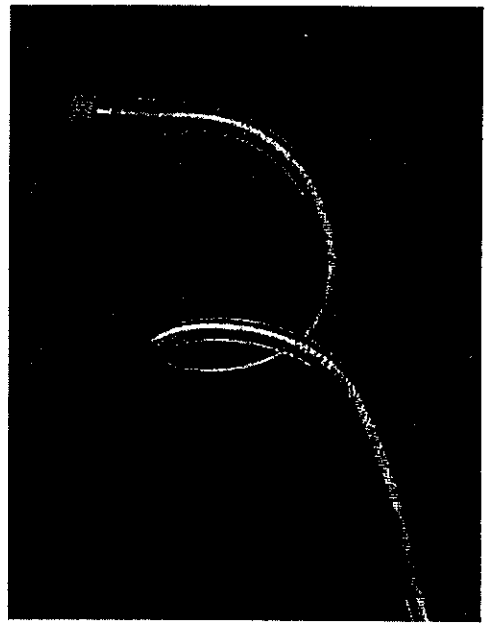
- an evaluation of the specific tachycardia rate(s)
- the confirmation and/or evaluation of any supraventricular arrhythmias or bradyarrhythmias
- the evaluation of various ATP and cardioversion therapies
- the presence of any post-shock arrhythmias, and
- an evaluation of the maximum sinus rate during exercise

If a patient's drug regimen is changed or adjusted while the CRT-D is implanted, additional EP testing may be required to determine if detection or therapy parameter settings are relevant and appropriate.

Empirical changes to the detection or therapy parameters should be assessed based on patient safety. Some changes may necessitate a re-assessment of sensing, pacing, or arrhythmia conversion treatment. Thorough technical knowledge of BIOTRONIK CRT-Ds, additional CRT-D or ICD experience, and individual medical judgment will aid in determining the need for additional testing and follow-up.

Corox OTW Steroid

Steroid-Eluting Left Ventricular Pacing Lead
IS-1 Connector



Technical Manual

BIOTRONIK

CAUTION

Federal (U.S.A.) law restricts this device to sale by, or on the order of, a physician.

Contents

1. Device Description

BIOTRONIK's Corox OTW Steroid leads are transvenous, steroid-eluting left ventricular pacing leads designed for use with a compatible cardiac resynchronization therapy (CRT) device that accepts leads with a unipolar (UP) IS-1 connector configuration. The lead can be positioned in the target vein using either the over-the-wire technique or a stylet.

The leads are constructed with multifilar conductors insulated with medical grade silicone and coated with polyurethane. The distal end of the lead is helix shaped at the lead tip, which facilitates attachment of the lead to the coronary vein.

The distal tip of the Corox OTW Steroid lead consists of a steroid-eluting collar, containing 0.5 mg of dexamethasone acetate (DXA). Upon exposure to body fluids, the steroid elutes from the collar into the body tissue by diffusion.

The Corox OTW Steroid lead features a tip electrode with a fractal surface structure of iridium that provides a larger effective tissue interface. The electrode is comprised of a platinum/iridium alloy base.

The Corox OTW Steroid leads are available in the following configurations: Corox OTW 75-UP Steroid (77 cm in length) and Corox OTW 85-UP Steroid (87 cm in length).

CAUTION

Because of the numerous available 3.2 mm configurations, e.g., the IS-1 and VS-1 standards, lead/pulse generator compatibility should be confirmed with the pulse generator and/or lead manufacturer prior to the implantation of a pacing system.

NOTE:

IS-1, wherever stated in this manual, refers to the international standard, whereby leads and generators from different manufacturers are assured a basic fit. [Reference ISO 5841-3:1992(E)].

See Section 10 for technical specifications of the Corox OTW Steroid lead.

2. Indications for Use

The Corox OTW Steroid leads are intended for implantation via the coronary veins to provide long term cardiac pacing when used in conjunction with a compatible pulse generator.

3. Contraindications

The use of the Corox OTW Steroid lead is contraindicated under the following circumstances:

- Coronary sinus anomalies
- Tissue in the coronary sinus area that has been damaged by an infarction
- Any anomalies of the venous system that preclude transvenous implantation of the lead
- Patient cannot tolerate a single systemic dose of up to 0.65 mg of dexamethasone acetate (DXA)

4. Warnings and Precautions

The performance of a cardiac pacing system depends on proper interaction of its three components: the pulse generator, the lead(s), and the patient. Abnormalities or changes in the electrical properties of any of the three components, or their interfaces with each other, may directly affect function of the entire system. Correct lead implantation is critical to safe and effective performance of the pacing system.

The pacing system may cease to function at any time due to medical and/or technical complications:

Medical Complications
Medical complications of the pacemaker treatment may include, but are not limited to: fibrotic tissue formation, thrombosis, embolism, elevated thresholds, body rejection phenomena, cardiac tamponade, muscle and nerve stimulation, myocardial perforation, erosion of the pulse generator/lead through the skin, infection and pacemaker-induced dysrhythmia (some of which could be life-threatening such as ventricular fibrillation).

Technical Complications
Incorrect operation of the pacing system may be caused by but is not limited to: improper lead placement, lead dislodgement, lead fracture, loss of insulation integrity, battery depletion, or electrical component failure.

Potentially Harmful Therapeutic and Diagnostic Procedures
As an implanted pacing lead is a direct, low resistance path to the myocardium for electrical current, the observance of high standards of electrical safety is required. Electrosurgical instruments, for example, could generate voltages of such amplitude that a direct coupling between the tip of the electrocautery device and the implanted lead may result, possibly inducing myocardial lesions or serious cardiac arrhythmias (e.g., fibrillation).

Some therapeutic and diagnostic procedures (e.g., diathermy, MRI, electrocautery) may result in latent damage to the pacing system. This damage may not be detected when testing the pulse generator function immediately after the procedure, but may become evident at a later time, resulting in pacing system malfunction or failure.

Prevention of Leakage Current Conduction
Pulse generators and testing equipment connected to the lead must be battery-powered. Proper grounding of line-powered devices in the vicinity of the patient is essential to prevent leakage currents arising from such devices to be conducted via the lead's terminal or any other non-insulated part.

Previously Implanted Leads
It is generally recommended that a chronically implanted lead not be explanted. If it becomes necessary to abandon a lead, the connector pin should be capped to prevent the transmission of electrical signals to the heart.

Storage Temperature
Recommended storage temperature range is 5°– 25° C (41°–77° F). The lead may be stored at a maximum temperature of 50°C (122°F) for only one month. Exposure to temperatures outside this range may result in lead malfunction.

Necessary Equipment for Implantation
During implantation the ECG should be recorded; a pacing system analyzer (PSA) and defibrillation equipment should always be readily available.

Handling the Lead
The lead should be handled very carefully at all times. Any severe application of force (bending, stretching, crimping, etc.) may permanently damage the lead. The metal portion of the lead connector should not be touched.

Lead Lumen
The inner lumen of the Corox OTW Steroid lead may not be rinsed with irrigation solution under any circumstances. The resulting excessive pressure inside the lead could damage the silicone insulation.

Stylet Insertion
To avoid damage to the lead, do not insert the stylet too rapidly nor use excessive force when inserting the stylet into the lead.

Only use stylets suitable for the Corox OTW Steroid leads. Using unsuitable leads can damage the lead or protrude over the tip electrode and cause injury to the patient.

Lead/Pulse Generator Compatibility
Because of the numerous available 3.2 mm configurations, e.g., the IS-1 and VS-1 standards, lead/pulse generator compatibility should be confirmed with the pulse generator and/or lead manufacturer prior to the implantation of a pacing system.

NOTE:

IS-1, wherever stated in this manual, refers to the international standard, whereby leads and generators from different manufacturers are assured a basic fit. [Reference ISO 5841-3:1992(E)].

Anchoring Sleeve
Always use an anchoring sleeve (lead fixation sleeve) when implanting a lead. Use of the anchoring sleeve, which is provided with the lead, will lessen the possibility of lead dislodgement and protect the lead body from damage by a securing ligature.

Measuring Intracardiac Signals
Depending on the PSA used, pacing may be interrupted during the measurement of the intracardiac signals. BIOTRONIK's ERA 300 Pacing System Analyzer has back-up VVI pacing at a rate of 30 ppm during the intracardiac measurements.

Chronic Repositioning
It is generally recommended that a chronically implanted lead not be explanted. Chronic repositioning or removal of active fixation leads may be difficult due to the presence of blood or fibrotic tissue in the helix. If it becomes necessary to abandon a lead, the connector pin should be capped to prevent the transmission of electrical signals to the heart.

Setscrew Adjustment
The pulse generator's setscrew(s) must be retracted prior to inserting the lead connector. Failure to back off the pulse generator's setscrew(s) may result in damage to the lead(s), and/or difficulty connecting the lead(s).

Cross-Threading Setscrew
To prevent cross-threading the setscrew, do not back the setscrew completely out of the threaded hole. Leave the torque wrench in the slot of the setscrew while the lead is inserted.

Tightening Setscrew
Do not over-tighten the setscrew(s). Use only a torque wrench, which automatically prevents over-tightening.

Sealing Caps
For pacemakers requiring sealing caps, secure a sealing cap over the setscrew(s) to prevent pacemaker malfunction.

5. Adverse Events

5.1 Potential Adverse Events

Potential complications resulting from the use of left ventricular leads include, but are not limited to: thrombosis, embolism, body rejection phenomena, cardiac tamponade, pneumothorax, muscle/nerve stimulation, valve damage, fibrillation, infection, skin erosion and ventricular ectopy. Lead perforation through the myocardium has been rarely observed. The table below summarizes some of the potential symptoms indicating a complication and possible corrective actions:

Table 1: Potential Complications and Corrective Actions

Symptom	Potential Complication	Potential Corrective Action
Loss of pacing or sensing	Lead dislodgement	Reposition lead
	Lead fracture	Replace lead
	Setscrew penetration of lead insulation	Replace lead
	Improper lead / pulse generator connection	Reconnect lead to pulse generator
Increase/ decrease in threshold	Fibrotic tissue formation	Adjust pulse generator output; Replace/reposition lead

5.2 Observed Adverse Events

An outside the US clinical evaluation of the Corox OTW Steroid (OVID) involved a total of 132 patients meeting indications for biventricular pacing. The coronary sinus was accessed in all patients, and of these, 121 were successfully implanted with the Corox OTW Steroid LV lead. The cumulative implant duration was 1145 months with a mean duration of 9.6 months. Ninety-six (79%) of the patients have implant durations greater than 6 months.

Of the 44 adverse events reported, there were 28 observations and 16 complications in a total of 132 patients. Table 2 and Table 3 provide a summary by category of each type of adverse event (complications and observations).

Table 2: Summary of Complications

Category	# of Pts	Percentage of Patients	# of Complications	Complication per pt-year
Corox OTW Steroid Lead-Related				
Loss of capture	5	3.8%	5	0.05
Phrenic nerve stimulation	2	1.5%	2	0.02
Total LV Lead Related	7	5.3%	7	0.07
Atrial Lead Related				
Loss of capture	2	1.5%	2	0.02
Total Atrial Lead Related	2	1.5%	2	0.02
RV Lead Related				
Loss of capture	3	2.3%	3	0.03
Elevated Pacing thresholds	2	1.5%	2	0.02
Total RV Lead Related	5	3.8%	5	0.05
Medical				
Arrhythmias	1	0.8%	1	0.01
Pocket infection	1	0.8%	1	0.01
Total Medical	2	1.5%	2	0.02
Overall Complication Totals	**13**	**9.8%**	**16**	**0.17**

Number of Patients = 132; Number of Patient-Years = 94.1

Table 3: Summary of Observations

Category	# of Pts	Percentage of Patients	# of Observations	Observation per pt-year
Corox OTW Steroid Lead-Related				
Implant failure	11	8.3%	11	0.12
Phrenic nerve stimulation	4	3.0%	4	0.04
Total LV Lead-Related	15	11.4%	15	0.16
Atrial Lead Related				
Loss of capture	1	0.8%	1	0.01
Elevated Pacing thresholds	1	0.8%	1	0.01
Total Atrial Lead Related	2	1.5%	2	0.02
RV Lead Related				
Elevated Pacing thresholds	2	1.5%	2	0.02
Total RV Lead Related	2	1.5%	2	0.02
Medical				
Arrhythmias	2	1.5%	2	0.02
Pocket infection/ Pericardial Effusion	2	1.5%	2	0.02
Chest pain	1	0.8%	1	0.01
Shortness of breath, palpitations	1	0.8%	1	0.01
Total Medical	6	4.5%	6	0.06
Miscellaneous				
Malfunction of hemostatic valve	2	1.5%	2	0.02
Improper Lead preparation	1	0.8%	1	0.01
Total Miscellaneous	3	2.3%	3	0.03
Overall Observation Totals	**26**	**19.7%**	**28**	**0.30**

Number of Patients = 132; Number of Patient-Years = 94.1

There were a total of 12 patient deaths reported in the OVID study. The clinical investigators determined that no deaths were related to the Corox OTW Steroid LV lead.

6. Clinical Studies

BIOTRONIK conducted a prospective registry outside the United States (OUS) of the Corox OTW Steroid LV lead in a multi-center trial with legally marketed CRT-D and CRT-P pulse generators that provide biventricular pacing therapy. Data from this registry is presented in the following sections to support the safety and efficacy of the Corox OTW Steroid LV lead.

6.1 Methods

The multi-center investigation was designed to validate the safety of the Corox OTW Steroid LV lead through a comparison of successfully implanted LV leads against a pre-defined success rate threshold, when no anatomical restrictions prevent access to the coronary sinus. The evaluation of safety is based on the analysis of the incidence of Corox OTW Steroid LV lead related adverse events, defined as any complications or observations judged by the investigator to be in probable relationship with Corox OTW Steroid LV lead system. Additionally, the effectiveness of the leads was evaluated using lead parameter data, including sensing amplitudes, pacing thresholds, and impedance values.

Inclusion Criteria

To support the objectives of this investigation, patients were required to meet the following inclusion criteria prior to enrollment:

- Meet the indications for bi-ventricular pacing
- Age ≥ 18 years
- Receiving optimal drug therapy for Congestive Heart Failure treatment
- Give informed consent

Exclusion Criteria

To support the objectives of this investigation, the exclusion criteria at the time of patient enrollment included the following requirements:

- Myocardial infarction or unstable angina pectoris
- Acute myocarditis
- Life expectancy ≤ 6 months
- Planned cardiac surgical procedures or interventional measures within the next 6 months
- Pregnancy

6.2 Overall Results

The Corox OTW Steroid LV clinical evaluation included a total of 132 patients meeting indications for biventricular pacing. The coronary sinus was accessed in all patients, and of these, 121 were successfully implanted with the Corox OTW Steroid LV lead. The study population ranged in age from 34 to 84 and included 99 males (75%) and 33 females (25%).

- The cumulative implant duration is 1145 months with a mean duration of 9.6 months. Ninety-six (79%) of the patients have implant durations greater than 6 months.
- The implant success rate for the Corox OTW/Steroid LV lead was 91.7% overall.
- The Corox OTW/Steroid LV lead was implanted in combination with 8 different CRT P and CRT D devices marketed by 4 different manufacturers.
- The mean LV pacing threshold at implant was 0.97 volts and at 6-months was 0.92 volts.
- The mean R-wave at implant was 15 mV.
- The mean LV lead impedance at implant was 796 ohms and at 6-months was 593 ohms.
- There have been 44 adverse events (28 observations in 26 patients and 16 complications in 13 patients). There have been no unanticipated adverse device effects reported.

- There have been 12 patient deaths reported in the OVID study. The clinical investigators have determined that no deaths were related to the Corox OTW/Steroid LV lead.
- The overall follow-up compliance rate for the OVID study is 92.9%.

6.2.1 Primary Endpoint

132 patients were enrolled in the study, and the coronary sinus was accessed in all patients. Corox OTW Steroid LV leads were successfully placed in 121 patients, which corresponds to an implantation success rate of 91.7% (95%-confidence interval: 0.86 – 0.96). Table 4 provides the Corox OTW Steroid implantation success rates within the clinical study.

Table 4: Corox OTW Steroid Implantation Success

Results	N	95% Confidence Interval
Coronary Sinus(CS) Found	132 of 132 (100%)	0.97 to 1.0
Successful implantations	121 of 132 (91.7%)	0.86 to 0.96
Success rate when CS was found	121 of 132 (91.7%)	0.86 to 0.96

Corox OTW Steroid LV lead implantation was not successful in 11 of 132 (8.3%) patients enrolled into the study. Details for these unsuccessful implant procedures are described in Table 5.

Table 5: Reasons for Implant Failure of Corox OTW Steroid LV lead

Reason for Implant Failure of Corox OTW/Steroid LV lead	N
Inability to find a stable position	3 of 132 (2.3%)
Target position not reached	3 of 132 (2.3%)
Coronary vessels too small	2 of 132 (1.5%)
Lead dislodged while removing guide catheter	2 of 132 (1.5%)
Perforation of SVC with pneumothorax	1 of 132 (0.8%)
Total Implant Failures of LV lead	**11 (8.3%)**

Objective: The lower bound of the one-sided 95% confidence interval of the successful implantation rate of the BIOTRONIK Corox OTW Steroid LV lead will not be less than 67%. The success rate was defined as a proportion of patients who received the Corox OTW Steroid LV lead during implantation when adequate left ventricular stimulation by the Corox OTW Steroid LV lead was confirmed after having finished the implantation procedure.

Results: One hundred and thirty-two patients were enrolled into the clinical study and a Corox OTW Steroid LV lead implant was attempted for each. One hundred and twenty-one patients were successfully implanted. The rate of successful implant of the Corox OTW Steroid LV lead is 91.7% with a lower 95% confidence bound of 86%. The lower 95% confidence bound of the implant success rate exceeds the limit of 67% and therefore, the null hypothesis is rejected. These results demonstrate that the Corox OTW Steroid LV lead has an appropriate implant success rate.

6.2.2 Secondary Endpoints

Reported lead data reflect only the patients with successfully implanted LV leads. LV sensing measurements were performed at implant only because LV sensing cannot be measured through the pulse generators used in the study. These values were all clinically acceptable for LV leads, with an average R-wave amplitude of 15 ± 7 mV. Lead impedance values were collected and also were all clinically acceptable, with an average pacing impedance of 590 ± 136 Ohms at 3 months. Table 6 provides a summary of the pacing thresholds at implant, one month and three months.

Table 6: Ventricular Pacing Thresholds – Corox OTW Steroid LV Lead

Pacing Threshold	Results (Volts @ 0.50 ms)
Implant	
Number of Tests	114
Mean ± SD	0.98 ± 0.8
Range	0.2 - 4.0
One-month Follow-up	
Number of Tests	72
Mean ± SD	0.94 ± 0.7
Range	0.3 - 3.9
Three-month Follow-up	
Number of Tests	71
Mean ± SD	0.89 ± 0.7
Range	0.2 - 3.8

There were 8 LV lead related complications (including the pocket infection which could not be ruled out as related) in 121 patients successfully implanted with the Corox OTW/Steroid LV lead through six months follow-up. The freedom from Corox OTW/Steroid LV lead-related complications is 92.9% with a two-sided lower 95% confidence bound of 86.4%

The complication and observation adverse event rates for the Corox OTW Steroid LV lead were 5.3% and 11.4%, respectively during the clinical study. Both these rates are acceptable for prospective biventricular LV pacing lead trials. Furthermore, the overall complication and observation adverse event rates for the patients were 9.8% and 19.7% respectively. This data demonstrates the overall safety performance profile of the Corox OTW Steroid LV lead.